

# SEARCH REQUEST FORM

127547

Requestor's Name: Rimualook

Serial Number: 291 853 619

Date: 7/19/04

Phone: Rem 460

Art Unit: 1614

MEJ

## Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Inv Rangaswamy Govindarajan

Please search the

1. immodane to treat a) colon cancer  
b) " rectal "
2. immodane to treat a + b.
3. use of immodane to limit/reduce side effects caused by chem agents
4. use of immodane to treat diarrhea
5. Structures of 1 + 2.
6. use of immodane to potentiate chem agents

} doses of each

Thanks

Rimualook

7/20/04  
16:00

## STAFF USE ONLY

Date completed: 7-20-04  
Searcher: POB  
Terminal time: 74  
Elapsed time: prep 20  
CPU time: \_\_\_\_\_  
Total time: \_\_\_\_\_  
Number of Searches: \_\_\_\_\_  
Number of Databases: \_\_\_\_\_

Search Site  
\_\_\_\_ STIC  
\_\_\_\_ CM-1  
\_\_\_\_ Pre-S  
Type of Search  
\_\_\_\_ N.A. Sequence  
\_\_\_\_ A.A. Sequence  
\_\_\_\_ Structure  
8 Bibliographic

Vendors  
\_\_\_\_ IG  
391 STN  
\_\_\_\_ Dialog  
\_\_\_\_ APS  
\_\_\_\_ Geninfo  
\_\_\_\_ SDC  
\_\_\_\_ DARC/Questel  
\_\_\_\_ Other

Location Log  
Duplicate Request \_\_\_\_\_  
NPL \_\_\_\_\_ MIC \_\_\_\_\_ Adonis \_\_\_\_\_  
BioTech Lib \_\_\_\_\_ Main \_\_\_\_\_  
NOX NOS VOLNO \_\_\_\_\_  
Ck Cite \_\_\_\_\_ INIT W Call #: \_\_\_\_\_

STIC-ILL

504396

From: Cook, Rebecca  
Sent: Monday, July 19, 2004 5:44 PM  
To: STIC-ILL  
Subject: 09/853,619

7/20

pls send me

Marx  
proc am soc clin oncology  
1999, 18, 454a

thank you

Rebecca Cook  
Rem 4C70

with  
8/8/48

=> fil reg; d ide

FILE 'REGISTRY' ENTERED AT 12:05:06 ON 20 JUL 2004

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 19 JUL 2004 HIGHEST RN 713066-32-1

DICTIONARY FILE UPDATES: 19 JUL 2004 HIGHEST RN 713066-32-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:  
<http://www.cas.org/ONLINE/DBSS/registryss.html>

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 97682-44-5 REGISTRY

CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline, [1,4'-bipiperidine]-1'-carboxylic acid deriv.

CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, (S)-

OTHER NAMES:

CN (+)-Irinotecan

CN Camptosar

CN **Irinotecan**

FS STEREOSEARCH

MF C33 H38 N4 O6

CI COM

SR CA

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK\*, PROMT, PROUSDDR, PS, RTECS\*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

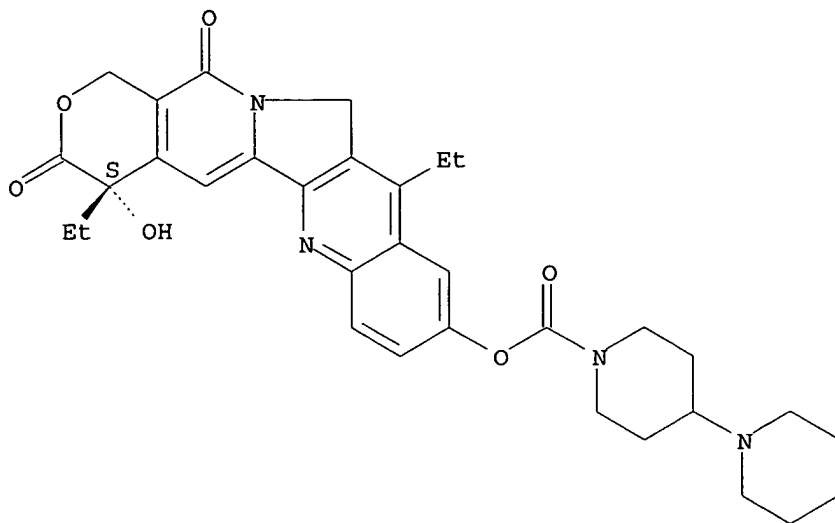
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological

study); PREP (Preparation); PROC (Process); USES (Uses)

Absolute stereochemistry. Rotation (+).



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

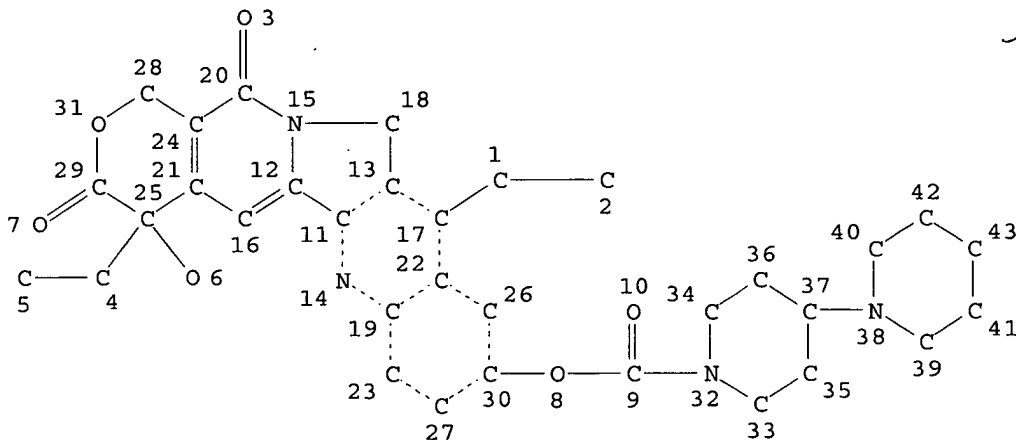
928 REFERENCES IN FILE CA (1907 TO DATE)

25 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

932 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d stat que 14

L2 STR



*family search done  
on structure of  
Irinotecan to retrieve  
exact substances,  
stereoisomers, salts,  
multicomponent  
substances, &  
isotopically labelled forms*

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 43

STEREO ATTRIBUTES: NONE

L4 10 SEA FILE=REGISTRY FAM FUL L2

100.0% PROCESSED 34 ITERATIONS  
SEARCH TIME: 00.00.01

10 ANSWERS

=> d ide

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 50-35-1 REGISTRY

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phthalimide, N-(2,6-dioxo-3-piperidyl)- (6CI, 7CI, 8CI)

OTHER NAMES:

CN (.+-.)-Thalidomide

CN .alpha.-(N-Phthalimido)glutarimide

CN .alpha.-N-Phthalylglutaramide

CN .alpha.-Phthalimidoglutaramide

CN 1,3-Dioxo-2-(2,6-dioxopiperidin-3-yl)isoindoline

CN 3-Phthalimidoglutaramide

CN Celgene

CN Contergan

CN Distaval

CN K 17

CN Kevadon

CN Myrin

CN N-(2,6-Dioxo-3-piperidyl)phthalimide

CN N-Phthaloylglutamimide

CN Neurosedyn

CN NSC 527179

CN NSC 66847

CN Pantosediv

CN Quetimid

CN Sedalis

CN Sedoval

CN Softenil

CN Softenon

CN Suaramide

CN Talimol

CN Talinol

CN **Thalidomide**

CN Thalomid

FS 3D CONCORD

DR 14088-68-7, 731-40-8

MF C13 H10 N2 O4

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN\*,  
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS,  
CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,  
DIOGENES, DRUGU, EMBASE, HODOC\*, HSDB\*, IMSCOSEARCH, IMSDRUGNEWS,  
IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK\*, MSDS-OHS, NIOSHTIC, PHAR,  
PIRA, PROMT, PROUSDDR, PS, RTECS\*, SPECINFO, SYNTHLINE, TOXCENTER, USAN,  
USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: EINECS\*\*, WHO

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

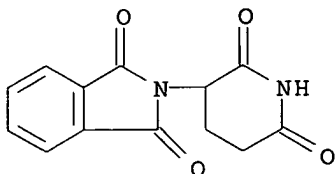
DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); PREP

(Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)  
 RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

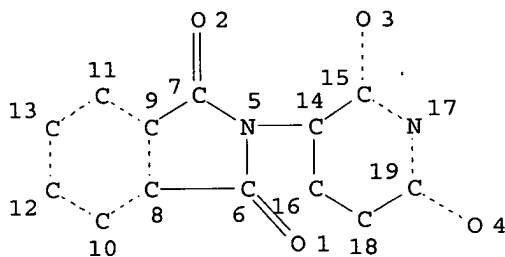


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1631 REFERENCES IN FILE CA (1907 TO DATE)  
 97 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 1640 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
 15 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d stat que  
 L6

STR



*family search done  
 on structure of Thalidomide*

NODE ATTRIBUTES:  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
 RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE  
 L8 66 SEA FILE=REGISTRY FAM FUL L6

100.0% PROCESSED 138 ITERATIONS  
 SEARCH TIME: 00.00.01

66 ANSWERS

=> fil medl; d que l25; d que l32; d que l35  
 FILE 'MEDLINE' ENTERED AT 13:14:16 ON 20 JUL 2004

FILE LAST UPDATED: 17 JUL 2004 (20040717/UP). FILE COVERS 1951 TO DATE.

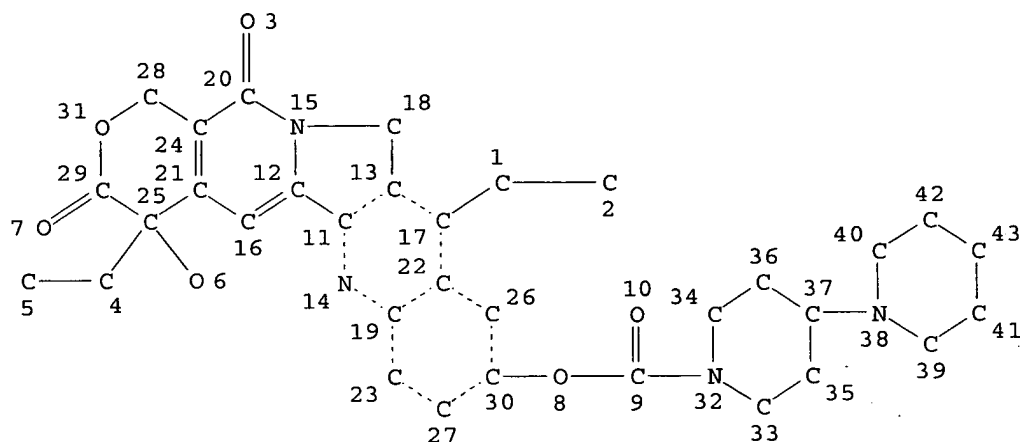
On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L2

STR



NODE ATTRIBUTES:  
 DEFAULT MLEVEL IS ATOM  
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
 RING(S) ARE ISOLATED OR EMBEDDED  
 NUMBER OF NODES IS 43

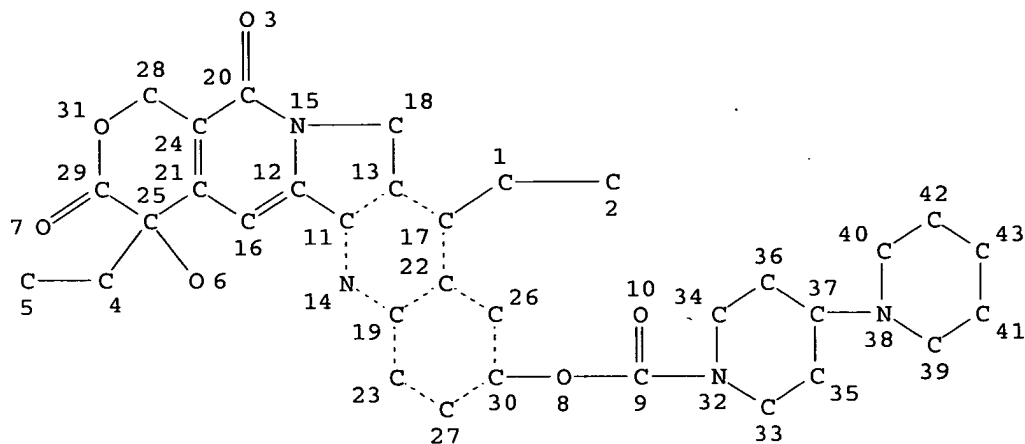
STEREO ATTRIBUTES: NONE

L4	10	SEA FILE=REGISTRY FAM FUL L2
L13	2298	SEA FILE=MEDLINE ABB=ON L4 OR IRINOTECAN OR CPT 11 OR CPT11 OR SN 38 11 OR SN3811 OR CAMPTOTHECIN 11 OR CAMPTOSAR#
L14	77610	SEA FILE=MEDLINE ABB=ON COLORECTAL NEOPLASMS+NT/CT
L16	2320	SEA FILE=MEDLINE ABB=ON CAMPTOTHECIN/CT(L) AA/CT
L17	1281	SEA FILE=MEDLINE ABB=ON L16/MAJ AND L13
L19	12633	SEA FILE=MEDLINE ABB=ON L14(L) (DT OR PC)/CT
L20	7778	SEA FILE=MEDLINE ABB=ON L19/MAJ
L21	335	SEA FILE=MEDLINE ABB=ON L17 AND L20
L22	1066	SEA FILE=MEDLINE ABB=ON CAMPTOTHECIN/CT(L) AD/CT
L23	148	SEA FILE=MEDLINE ABB=ON L22/MAJ
L24	30	SEA FILE=MEDLINE ABB=ON L21 AND L23
L25	8	SEA FILE=MEDLINE ABB=ON DOS####/TI AND L24

*Subheadings*  
 AA - analogs & derivatives  
 DT - drug therapy  
 PC - prevention & control  
 AD - administration & dosage



L2 STR



## NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 43

## STEREO ATTRIBUTES: NONE

L4 10 SEA FILE=REGISTRY FAM FUL L2

L13 2298 SEA FILE=MEDLINE ABB=ON L4 OR IRINOTECAN OR CPT 11 OR CPT11  
OR SN 38 11 OR SN3811 OR CAMPTOTHECIN 11 OR CAMPTOSAR#

L14 77610 SEA FILE=MEDLINE ABB=ON COLORECTAL NEOPLASMS+NT/CT

L16 2320 SEA FILE=MEDLINE ABB=ON CAMPTOTHECIN/CT(L) AA/CT

L17 1281 SEA FILE=MEDLINE ABB=ON L16/MAJ AND L13

L19 12633 SEA FILE=MEDLINE ABB=ON L14(L) (DT OR PC)/CT

L20 7778 SEA FILE=MEDLINE ABB=ON L19/MAJ

L21 335 SEA FILE=MEDLINE ABB=ON L17 AND L20

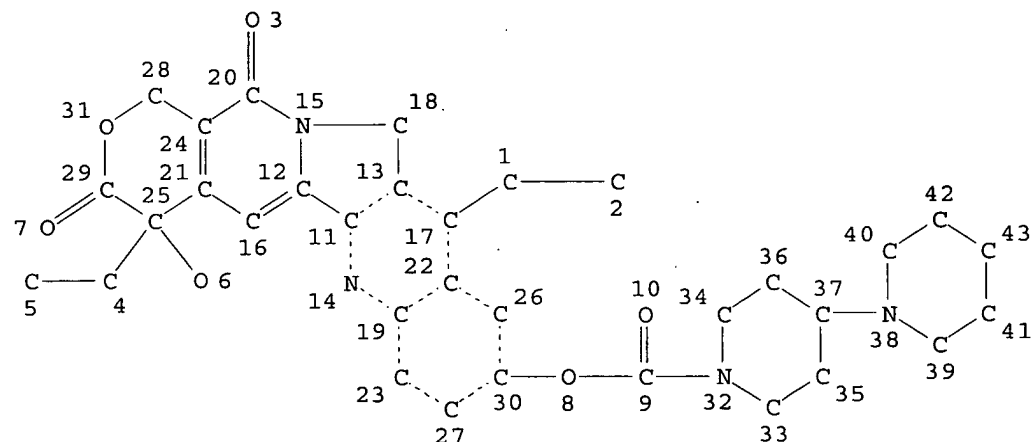
L26 204314 SEA FILE=MEDLINE ABB=ON DOSE-RESPONSE RELATIONSHIP, DRUG/CT

L27 47600 SEA FILE=MEDLINE ABB=ON DRUG ADMINISTRATION SCHEDULE+NT/CT

L31 22 SEA FILE=MEDLINE ABB=ON L21 AND L26 AND L27

L32 2 SEA FILE=MEDLINE ABB=ON GENERAL REVIEW/DT AND L31

L2 STR



## NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

## GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 43

## STEREO ATTRIBUTES: NONE

L4 10 SEA FILE=REGISTRY FAM FUL L2  
L13 2298 SEA FILE=MEDLINE ABB=ON L4 OR IRINOTECAN OR CPT 11 OR CPT11  
OR SN 38 11 OR SN3811 OR CAMPTOTHECIN 11 OR CAMPTOSAR#  
L14 77610 SEA FILE=MEDLINE ABB=ON COLORECTAL NEOPLASMS+NT/CT  
L16 2320 SEA FILE=MEDLINE ABB=ON CAMPTOTHECIN/CT(L)AA/CT  
L17 1281 SEA FILE=MEDLINE ABB=ON L16/MAJ AND L13  
L19 12633 SEA FILE=MEDLINE ABB=ON L14(L) (DT OR PC)/CT  
L20 7778 SEA FILE=MEDLINE ABB=ON L19/MAJ  
L21 335 SEA FILE=MEDLINE ABB=ON L17 AND L20  
L22 1066 SEA FILE=MEDLINE ABB=ON CAMPTOTHECIN/CT(L)AD/CT  
L26 204314 SEA FILE=MEDLINE ABB=ON DOSE-RESPONSE RELATIONSHIP, DRUG/CT  
L27 47600 SEA FILE=MEDLINE ABB=ON DRUG ADMINISTRATION SCHEDULE+NT/CT  
L33 22 SEA FILE=MEDLINE ABB=ON L21 AND (L26 OR L27) AND GENERAL  
REVIEW/DT  
L35 17 SEA FILE=MEDLINE ABB=ON L33 AND L22

=&gt; s l25 or l32 or l35

L124 25 L25 OR L32 OR L35

=&gt; d iall l124 1-25

L124 ANSWER 1 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2004272642 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 15170977  
TITLE: Chemotherapy.  
AUTHOR: Aiba Keisuke  
CORPORATE SOURCE: Dept. of Internal Medicine, Clinical Oncology Program,  
Jikei University School of Medicine, 3-25-8  
Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan.  
SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2004 May) 31  
(5) 706-11. Ref: 32  
Journal code: 7810034. ISSN: 0385-0684.  
PUB. COUNTRY: Japan  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: Japanese  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200406  
ENTRY DATE: Entered STN: 20040603  
Last Updated on STN: 20040609  
Entered Medline: 20040608

## ABSTRACT:

Cancer chemotherapy in the treatment of colorectal cancer has been evolving so extensively than ever. 5-fluorouracil (5-FU) has been a pivotal and a single active agent in the treatment of colorectal cancer. Reproducing and consistent better response rate has been shown since the introduction of the concept of biochemical modulation of 5-FU by leucovorin, a reduced folate, to the clinic and a combination chemotherapy of 5-FU and leucovorin (FL) has enable us to obtain a response rate around 20-30% and a median survival time ranging from 10 to 12 months. IFL regimen combing CPT-11 with FL showed a

better MST ranging from 14 to 15 months, but now serious toxicity precludes general use outside of clinical trials. In the Europe, de Gramont regimen, an unique dose and schedule of 5-FU using a combination of continuous intravenous infusion of 5-FU with leucovorin over two days and bolus infusion of 5-FU twice over the same period, has been developed and shown improved antitumor activity and toxic profiles. FOLFOX 4, a combination chemotherapy of de Gramont regimen and oxaliplatin which is a third generation of cisplatin and a unique toxic profile with neuropathy, has demonstrated improved MST over a year and acceptable toxic profiles. Now FOLFOX 4 is considered to be a standard chemotherapy for the patients with advanced colorectal cancer, since a large phase III randomized study has shown that FOLFOX 4 was the most active and less toxic treatment regimen among active regimens such as IFL and IROX (CPT-11 and oxaliplatin). More recently, a combination of IFL and bevacizumab which is one of the molecular target agents and a antibody agent against vascular endothelial growth factor (VEGF), has demonstrated better MST reaching 20 months. Future large scale trials will attempt to develop more active regimen incorporating so-called molecular target agents.

CONTROLLED TERM: Check Tags: Human

Antineoplastic Combined Chemotherapy Protocols: AD,  
administration & dosage

\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use

Camptothecin: AD, administration & dosage

\*Camptothecin: AA, analogs & derivatives

Clinical Trials, Phase III

\*Colorectal Neoplasms: DT, drug therapy

Drug Administration Schedule

English Abstract

Fluorouracil: AD, administration & dosage

Leucovorin: AD, administration & dosage

Organoplatinum Compounds: AD, administration & dosage

Randomized Controlled Trials

Survival Analysis

Treatment Outcome

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 51-21-8 (Fluorouracil);  
58-05-9 (Leucovorin); 63121-00-6 (oxaliplatin); 7689-03-4  
(Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0  
(Folfox protocol); 0 (Organoplatinum Compounds)

L124 ANSWER 2 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2004153519 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15045956

TITLE: A case of highly advanced ascending colon cancer with  
multiple bone and liver metastases and pleuritis  
carcinomatosa treated with pharmacokinetic modulating  
chemotherapy and low-dose CPT-  
11.

AUTHOR: Yagyu Toshihiko; Aihara Tsukasa; Murayama Michinori;  
Nakamura Eisyu; Nozaki Hideto; Niida Masakuni; Yasuoka  
Hiroki; Nishimoto Yutaka; Watanabe Yoshinori; Syouda  
Shinichi; Kouno Toshihiko; Fukuhara Akinori; Nakagawa  
Katsuya

CORPORATE SOURCE: Dept. of Surgery, Japan Self Defense Force Hanshin  
Hospital.

SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2004 Mar) 31  
(3) 431-3.

Journal code: 7810034. ISSN: 0385-0684.

PUB. COUNTRY: Japan

DOCUMENT TYPE: (CASE REPORTS)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: Japanese

FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200404  
ENTRY DATE: Entered STN: 20040330  
Last Updated on STN: 20040403  
Entered Medline: 20040402

## ABSTRACT:

A 54 year-old male was admitted for highly advanced ascending colon cancer with multiple bone and liver metastases and pleuritis carcinomatosa. He was treated with pharmacokinetic modulating chemotherapy (PMC) and low-dose CPT-\*\*\*11\*\*\*. UFT (400 mg) was orally administered daily and a 2-hour infusion of l-leucovorin (250 mg/m2/day) with a continuous infusion of 5-FU (600 mg/m2/24 h) was given once a week on an outpatient basis. CPT-\*\*\*11\*\*\* (80 mg/body/2 h) was administered every 2 weeks. Partial response was obtained in the liver for 6 months and in the primary lesion for 9 months. Significant decrease of pain from the multiple bone metastases was observed for 4 months without severe side effects, which led to an improvement in performance status and quality of life for the patient. He survived more than 11 months after initial treatment. The duration of his stay at home was 288 days, accounting for 83% of the treatment period. This case suggests the efficacy of home anticancer therapy with PMC and low-dose CPT-\*\*\*11\*\*\* for highly advanced colon cancer in terms of QOL.

CONTROLLED TERM: Check Tags: Human; Male  
\*Adenocarcinoma: DT, drug therapy  
Adenocarcinoma: SC, secondary  
\*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use  
\*Bone Neoplasms: SC, secondary  
\*Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
\*Colonic Neoplasms: DT, drug therapy  
Colonic Neoplasms: PA, pathology  
Dose-Response Relationship, Drug  
Drug Administration Schedule  
Drug Combinations  
English Abstract  
Fluorouracil: AD, administration & dosage  
Leucovorin: AD, administration & dosage  
\*Liver Neoplasms: SC, secondary  
Middle Aged  
\*Pleurisy: DT, drug therapy  
Pleurisy: ET, etiology  
Quality of Life  
Tegafur: AD, administration & dosage  
Uracil: AD, administration & dosage  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 17902-23-7 (Tegafur);  
51-21-8 (Fluorouracil); 58-05-9 (Leucovorin); 66-22-8 (Uracil); 7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Drug Combinations); 0 (UFT(R) drug)

L124 ANSWER 3 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2004109537 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 14999538  
TITLE: Pilot study of low-dose, divided maximum tolerated dose of CPT-11 in 21 consecutive patients with metastatic colorectal or gastric cancer.  
AUTHOR: Takahashi Yutaka; Kitakata Hidekazu; Yamashita Kaname; Yasumoto Kazuo; Omote Kazuhiko; Minamoto Toshinari; Mai Masayoshi  
CORPORATE SOURCE: Department of Surgical Oncology, Cancer Research Institute, Kanazawa University, 13-1 Takaramachi, Kanazawa 920-8641,

SOURCE: Japan.  
Surgery today, (2004) 34 (3) 246-50.  
Journal code: 9204360. ISSN: 0941-1291.  
PUB. COUNTRY: Japan  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200406  
ENTRY DATE: Entered STN: 20040305  
Last Updated on STN: 20040625  
Entered Medline: 20040624

## ABSTRACT:

PURPOSE: We devised a new treatment regimen, delivering a frequent low dose of \*\*\*CPT\*\*\* -11, calculated by dividing the maximum tolerated dose (MTD) to reduce its toxicity without impairing its efficacy. METHODS: CPI-11, 25 mg/m<sup>2</sup>, determined by dividing the MTD dose per month by 12, was given on days 1, 2, and 3 of every week, to 21 consecutive patients; 12 with metastatic colon cancer and 9 with metastatic gastric cancers. RESULTS: The total delivered dose of CPI-11 per patient was more than 1,000 mg in 17 (80.1%) of the 21 patients. Grade 3 marrow depression developed in 3 (14.3%) patients, and although nausea, vomiting, alopecia, and diarrhea developed in some patients, these side effects were all categorized as grade 2 or milder. The antitumor effect was evaluated in 18 patients with measurable lesions, who had received CPI-11 according to our regimen for at least 3 weeks. Of these 18 patients, 10, 7, and 1, respectively, had a found to have partial response, no change, or progression of disease, demonstrating a 55.6% efficacy rate [colon 6/10 (60.0%) and stomach 4/8 (50.0%)]. Moreover, time to progression (TTP) was greater than 90 days in 12 (75.0%) of these 18 patients. CONCLUSION: These results show that our low-dose, divided MTD of CPI-11 regimen is a promising method of reducing toxicity and strengthening the antitumor effect, justifying further large-scale comparative clinical studies to verify this potential.

CONTROLLED TERM: Check Tags: Female; Human; Male  
Aged  
Aged, 80 and over  
\*Antineoplastic Agents, Phytogenic: AD, administration & dosage  
Antineoplastic Agents, Phytogenic: TU, therapeutic use  
\*Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Camptothecin: TU, therapeutic use  
\*Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: PA, pathology  
Disease Progression  
Liver Neoplasms: SC, secondary  
Lung Neoplasms: SC, secondary  
Maximum Tolerated Dose  
Middle Aged  
Pilot Projects  
\*Stomach Neoplasms: DT, drug therapy  
Stomach Neoplasms: PA, pathology

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 7689-03-4  
(Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic)

L124 ANSWER 4 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2003498301 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 14574912  
TITLE: 5-fluorouracil and leucovorin therapy for advanced colorectal cancer.  
AUTHOR: Shimoyama Satofumi; Kondo Ken; Kataoka Masato  
CORPORATE SOURCE: Department of Surgery, Nagoya National Hospital.

SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2003 Sep) 61 Suppl 7 356-9. Ref: 13  
Journal code: 0420546. ISSN: 0047-1852.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: Japanese

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200401

ENTRY DATE: Entered STN: 20031025  
Last Updated on STN: 20040107  
Entered Medline: 20040106

CONTROLLED TERM: Check Tags: Human  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Clinical Trials  
\*Colorectal Neoplasms: DT, drug therapy  
Disease Progression  
Drug Administration Schedule  
Fluorouracil: AD, administration & dosage  
Japan  
Leucovorin: AD, administration & dosage  
\*Neoplasm Recurrence, Local: DT, drug therapy  
Organoplatinum Compounds: AD, administration & dosage  
United States

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 51-21-8 (Fluorouracil);  
58-05-9 (Leucovorin); 63121-00-6 (oxaliplatin); 7689-03-4  
(Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0  
(Organoplatinum Compounds)

L124 ANSWER 5 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2003493328 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14569847

TITLE: Improving the toxicity of irinotecan  
/5-FU/leucovorin: a 21-day schedule.

AUTHOR: Hwang Jimmy J; Eisenberg Steven G; Marshall John L

CORPORATE SOURCE: Lombardi Cancer Center, Georgetown University Medical  
Center, Washington, DC, USA.. jh96@georgetown.edu

SOURCE: Oncology (Williston Park, N.Y.), (2003 Sep) 17 (9 Suppl 8)  
37-43. Ref: 36  
Journal code: 8712059. ISSN: 0890-9091.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200402

ENTRY DATE: Entered STN: 20031023  
Last Updated on STN: 20040211  
Entered Medline: 20040210

## ABSTRACT:

Irinotecan (CPT-11, Camptosar) is one of the new generation of chemotherapeutic agents that has activity in advanced colorectal cancer. It has antitumor efficacy as a single agent, and also has been combined with fluorouracil (5-FU) and leucovorin (IFL) to treat these patients. Randomized studies have confirmed the superiority of IFL to 5-FU and leucovorin alone with regard to patient survival, time to progression, and

tumor response rate. The optimal schedule for combining these agents remains uncertain, but in the United States, the schedule of IFL weekly for 4 consecutive weeks repeated every 6 weeks, according to the schedule reported by Saltz et al, has been widely used, although with some toxicity (especially myelosuppression and diarrhea). In an attempt to improve the tolerability of IFL, some have advocated modifying the schedule of IFL to weekly for 2 weeks, with repeated cycles every 21 days. Twenty-three patients with advanced colorectal cancer have been treated on this schedule at a single institution. Therapy was well tolerated, with 35% of patients experiencing grade 3/4 neutropenia, two of whom had episodes of febrile neutropenia, and 9% with grade 3/4 diarrhea. The median relative dose intensity of **irinotecan** administered in the first 18 patients treated with this regimen was 94%. These data support the hypothesis that modifying the schedule of administration of IFL improves the tolerability and ability to deliver the regimen, but must be confirmed by randomized prospective studies, which may also attempt to evaluate the role of bolus 5-FU in the treatment of advanced colorectal cancer.

CONTROLLED TERM: Check Tags: Human  
\*Antineoplastic Combined Chemotherapy Protocols: AD,  
administration & dosage  
\*Antineoplastic Combined Chemotherapy Protocols: AE,  
adverse effects

**Camptothecin: AD, administration & dosage**

Camptothecin: AE, adverse effects

**\*Camptothecin: AA, analogs & derivatives**

Clinical Trials

**\*Colorectal Neoplasms: DT, drug therapy**

**Dose-Response Relationship, Drug**

Fluorouracil: AD, administration & dosage

Fluorouracil: AE, adverse effects

Leucovorin: AD, administration & dosage

Leucovorin: AE, adverse effects

Survival Analysis

CAS REGISTRY NO.: 100286-90-6 (**irinotecan**); 51-21-8 (Fluorouracil);  
58-05-9 (Leucovorin); 7689-03-4 (Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols)

L124 ANSWER 6 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2003457453 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14518404

TITLE: Controversy of treatment for advanced colorectal  
cancer--intermedisine.

AUTHOR: Sato Atushi; Shimada Ken; Taguchi Susumu

CORPORATE SOURCE: Department of Internal Medicine, Showa University Northern  
Yokohama Hospital, 35-1 Chigasaki-chuo, Tsuzuki-ku,  
Yokohama, Kanagawa 224-8503, Japan.

SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2003 Sep) 30  
(9) 1260-9. Ref: 46  
Journal code: 7810034. ISSN: 0385-0684.

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

**General Review; (REVIEW)**

(REVIEW, TUTORIAL)

LANGUAGE: Japanese

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310

ENTRY DATE: Entered STN: 20031002

Last Updated on STN: 20031008

Entered Medline: 20031007

#### ABSTRACT:

Until recently, few chemotherapy options were available to treat metastatic colorectal cancer. For years, the standard chemotherapy has been a Fluorouracil (5-FU) alone or 5-FU with leucovorin (LV) modulation. The newer cytotoxic

drugs irinotecan (CPT-11) and oxaliplatin (L-OHP) has generated further improvement in survival. Additionally, improvement in convenience of drug administration has been achieved with the development of oral fluoropyrimidines. In randomized trials, oral fluoropyrimidines were equally effective to bolus 5-FU and LV. Recently completed or ongoing clinical trials to study novel targeting agents have initiated a new generation of drug development such as angiogenesis inhibitors and epidermal growth factor inhibitors. Randomized trials will determine the impact of these newer agents on survival and quality of life.

CONTROLLED TERM: Check Tags: Human  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
    **Camptothecin: AD, administration & dosage**  
    **\*Camptothecin: AA, analogs & derivatives**  
    Clinical Trials, Phase II  
    Clinical Trials, Phase III  
    **\*Colorectal Neoplasms: DT, drug therapy**  
    **Drug Administration Schedule**  
    Drug Combinations  
    English Abstract  
    Fluorouracil: AD, administration & dosage  
    Leucovorin: AD, administration & dosage  
    Organoplatinum Compounds: AD, administration & dosage  
    Oxonic Acid: AD, administration & dosage  
    Pyridines: AD, administration & dosage  
    Tegafur: AD, administration & dosage

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 150863-82-4 (S 1  
(combination)); 17902-23-7 (Tegafur); 51-21-8  
(Fluorouracil); 58-05-9 (Leucovorin); 63121-00-6  
(oxaliplatin); 7689-03-4 (Camptothecin); 937-13-3 (Oxonic  
Acid)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Drug  
Combinations); 0 (Organoplatinum Compounds); 0 (Pyridines)

L124 ANSWER 7 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2003447822 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 14508723  
TITLE: Alternative schedules with irinotecan.  
AUTHOR: Diasio Robert  
CORPORATE SOURCE: Department of Pharmacology/Toxicology, University of  
Alabama Comprehensive Cancer Center, Birmingham, AL 35294,  
USA.

SOURCE: Seminars in oncology, (2003 Aug) 30 (4 Suppl 12) 18-24.  
Ref: 19  
Journal code: 0420432. ISSN: 0093-7754.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
    **General Review; (REVIEW)**  
    (REVIEW, TUTORIAL)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200310  
ENTRY DATE: Entered STN: 20030926  
Last Updated on STN: 20031022  
Entered Medline: 20031021

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
    **\*Camptothecin: AD, administration & dosage**  
    **\*Camptothecin: AA, analogs & derivatives**  
    Clinical Trials  
    **\*Colorectal Neoplasms: DT, drug therapy**



**Drug Administration Schedule**

Fluorouracil: AD, administration &amp; dosage

Leucovorin: AD, administration &amp; dosage

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 51-21-8 (Fluorouracil);  
58-05-9 (Leucovorin); 7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols)

L124 ANSWER 8 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2003402905 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12941200  
TITLE: Colorectal cancer: integrating oxaliplatin.  
AUTHOR: Louvet Christophe; de Gramont Aimery  
CORPORATE SOURCE: Service d'Oncologie, Hôpital St-Antoine, 184 rue du  
faubourg St-Antoine, 75012 Paris, France..  
christophe.louvet@sat.ap-hop-paris.fr  
SOURCE: Current treatment options in oncology, (2003 Oct) 4 (5)  
405-11. Ref: 16  
Journal code: 100900946. ISSN: 1527-2729.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200311  
ENTRY DATE: Entered STN: 20030828  
Last Updated on STN: 20031106  
Entered Medline: 20031105

**ABSTRACT:**

5-Fluorouracil (5-FU), used according to several types of administration and several modulations, remained the standard treatment of colorectal cancer for many years. . However, two major drugs (irinotecan and oxaliplatin) improved the therapeutic possibilities for this disease. Both drugs are active as a single agent, but they have a clear in vitro and in vivo synergistic antitumoral activity when combined with modulated 5-FU. Significant improvements in response rate, progression-free survival, and overall survival have been obtained by irinotecan/5-FU and oxaliplatin/5-FU combinations compared to 5-FU alone. Integrating these drugs in the therapeutic strategy of metastatic colorectal cancer treatment was a challenge for clinical trials. Second- and third-line treatments are often used, and these treatments are a large reason for the improvement in survival. Each patient who is able to receive several lines of therapy should be offered this strategy. Many attempts to optimize the results of these combinations have been performed. Although no definitive data show one drug to be better than the other, several arguments favored the oxaliplatin/5-FU combination as a first-line treatment of metastatic colorectal cancer. A better collaboration between surgeons and oncologists, based on the improvement of surgical techniques and highly active chemotherapeutic regimens, provides patients more strategies with curative intent in liver and lung metastatic disease. Progress in treating metastatic disease will hopefully translate into the improvement of cure rates when applied to adjuvant therapy. The tolerance of the oxaliplatin/5-FU combination allows for design regimens integrating new drugs, such as biologic modifiers.

CONTROLLED TERM: Check Tags: Female; Human; Male  
Adult  
Aged  
\*Antineoplastic Combined Chemotherapy Protocols: AD,  
administration & dosage  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Chemotherapy, Adjuvant  
Colectomy: MT, methods

**\*Colorectal Neoplasms: DT, drug therapy**  
Colorectal Neoplasms: MO, mortality  
**\*Colorectal Neoplasms: PA, pathology**  
Colorectal Neoplasms: SU, surgery  
**Dose-Response Relationship, Drug**  
**Drug Administration Schedule**  
Fluorouracil  
Leucovorin  
Middle Aged  
Neoplasm Staging  
**\*Organoplatinum Compounds: AD, administration & dosage**  
Organoplatinum Compounds: AE, adverse effects  
Prognosis  
Randomized Controlled Trials  
Risk Assessment  
Survival Analysis  
Treatment Outcome

CAS REGISTRY NO.: **100286-90-6 (irinotecan); 51-21-8 (Fluorouracil);**  
58-05-9 (Leucovorin); 63121-00-6 (oxaliplatin); 7689-03-4  
(Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0  
(Folfox protocol); 0 (Organoplatinum Compounds)

L124 ANSWER 9 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2003306412 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12833857  
TITLE: Recent advances in chemotherapy for digestive cancers with  
special references to gastric and colonic cancers.  
AUTHOR: Sawabu Norio  
CORPORATE SOURCE: Department of Internal Medicine and Medical Oncology,  
Cancer Research Institute, Kanazawa University.  
SOURCE: Nippon Shokakibyō Gakkai zasshi The Japanese journal of  
gastro-enterology, (2003 Jun) 100 (6) 645-52. Ref: 46  
Journal code: 2984683R. ISSN: 0446-6586.  
PUB. COUNTRY: Japan  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
LANGUAGE: Japanese  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200307  
ENTRY DATE: Entered STN: 20030702  
Last Updated on STN: 20030716  
Entered Medline: 20030715  
CONTROLLED TERM: Check Tags: Human  
**\*Antineoplastic Combined Chemotherapy Protocols: TU,**  
therapeutic use  
**Camptothecin: AD, administration & dosage**  
**\*Camptothecin: AA, analogs & derivatives**  
Cisplatin: AD, administration & dosage  
**\*Colonic Neoplasms: DT, drug therapy**  
**Drug Administration Schedule**  
Drug Combinations  
Drug Delivery Systems  
Fluorouracil: AD, administration & dosage  
Oxonic Acid: AD, administration & dosage  
Paclitaxel: AD, administration & dosage  
**\*Paclitaxel: AA, analogs & derivatives**  
Pyridines: AD, administration & dosage  
**\*Stomach Neoplasms: DT, drug therapy**  
**\*Taxoids**  
Tegafur: AD, administration & dosage

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 114977-28-5 (docetaxel); 150863-82-4 (S 1 (combination)); 15663-27-1 (Cisplatin); 17902-23-7 (Tegafur); 33069-62-4 (Paclitaxel); 51-21-8 (Fluorouracil); 7689-03-4 (Camptothecin); 937-13-3 (Oxonic Acid)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Drug Combinations); 0 (Pyridines); 0 (Taxoids)

L124 ANSWER 10 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2003282524 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12810453

TITLE: **Irinotecan** in metastatic colorectal cancer: dose intensification and combination with new agents, including biological response modifiers.

AUTHOR: Ducreux M; Kohne C-H; Schwartz G K; Vanhoefer U

CORPORATE SOURCE: Institut Gustave Roussy, Villejuif, France.

SOURCE: Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, (2003) 14 Suppl 2 ii17-23. Ref: 40

JOURNAL code: 9007735. ISSN: 0923-7534.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310

ENTRY DATE: Entered STN: 20030618

Last Updated on STN: 20031101

Entered Medline: 20031031

## ABSTRACT:

Phase I/II studies suggest that the combination of **irinotecan** with capecitabine is feasible and has promising activity. Diarrhea and neutropenia are dose limiting. Overall response rates (RRs) in the 40% to 60% range are seen from preliminary data. Work in progress is assessing the combination of **irinotecan** with UFT/leucovorin (LV). The use of **irinotecan** together with raltitrexed is also being investigated, as is its combination with oxaliplatin. Two phase II studies of **irinotecan** plus oxaliplatin in second-line patients report median survivals of 11-12 months. It seems possible to safely escalate the dose of single-agent **irinotecan** to 500 mg/m<sup>2</sup> in patients showing good tolerance of the drug. **Irinotecan** can be used in combination with LV5FU2 at doses up to 260 mg/m<sup>2</sup>, especially if only one bolus of 5-fluorouracil (5-FU) is given. Control of tumor growth is achieved in 90% of patients. Preliminary data suggest that regimens based on 5-FU/LV and **irinotecan** can safely be combined with the anti-epidermal growth factor receptor (EGFR) antibody cetuximab. In patients with EGFR-positive tumors, this may prove an effective means of increasing response rate or combating treatment resistance. Following evidence that COX-2 inhibition can slow progression in familial adenomatous polyposis, celecoxib is to be studied in metastatic colorectal cancer (CRC). In vitro, the cyclin-dependent kinase inhibitor flavopiridol enhances the induction of apoptosis by chemotherapy. Clinically, it can safely be administered with **irinotecan**, and studies in CRC are planned.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't

Antibodies, Monoclonal: AD, administration & dosage

\*Antineoplastic Agents, Phytogenic: AD, administration & dosage

\*Antineoplastic Combined Chemotherapy Protocols: AD, administration & dosage

Antineoplastic Combined Chemotherapy Protocols: AE, adverse effects

Antineoplastic Combined Chemotherapy Protocols: TU,

therapeutic use

\*Biological Response Modifiers: TU, therapeutic use

\*Camptothecin: AD, administration & dosage

\*Camptothecin: AA, analogs & derivatives

Clinical Trials

\*Colorectal Neoplasms: DT, drug therapy

\*Colorectal Neoplasms: PA, pathology

Deoxycytidine: AD, administration & dosage

\*Deoxycytidine: AA, analogs & derivatives

Drug Administration Schedule

Enzyme Inhibitors: AD, administration & dosage

Flavonoids: AD, administration & dosage

Fluorouracil: AD, administration & dosage

Isoenzymes: AI, antagonists & inhibitors

Leucovorin: AD, administration & dosage

Organoplatinum Compounds: AD, administration & dosage

Piperidines: AD, administration & dosage

Prostaglandin-Endoperoxide Synthase

Quinazolines: AD, administration & dosage

Thiophenes: AD, administration & dosage

Treatment Outcome

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 112887-68-0  
(raltitrexed); 146426-40-6 (flavopiridol); 154361-50-9  
(capecitabine); 51-21-8 (Fluorouracil); 58-05-9  
(Leucovorin); 63121-00-6 (oxaliplatin); 7689-03-4  
(Camptothecin); 951-77-9 (Deoxycytidine)

CHEMICAL NAME: 0 (Antibodies, Monoclonal); 0 (Antineoplastic Agents,  
Phytogenic); 0 (Antineoplastic Combined Chemotherapy  
Protocols); 0 (Biological Response Modifiers); 0 (Enzyme  
Inhibitors); 0 (Flavonoids); 0 (Isoenzymes); 0  
(Organoplatinum Compounds); 0 (Piperidines); 0  
(Quinazolines); 0 (Thiophenes); 0 (cetuximab); EC 1.14.99.-  
(cyclooxygenase 2); EC 1.14.99.1 (Prostaglandin-  
Endoperoxide Synthase)

L124 ANSWER 11 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2003194229 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12714877

TITLE: Irinotecan in the treatment of advanced  
colorectal cancer in patients pretreated with  
Fluorouracil-based chemotherapy: a study to determine  
recommendable therapeutic dosage.

AUTHOR: Vieitez Jose M; Carrasco Juan; Esteban Emilio; Fra Joaquin;  
Alvarez Elena; Muniz Isabel; Sala Marian; Buesa Jose M;  
Jimenez Lacave Angel

CORPORATE SOURCE: Servicio de Oncologia Medica, Hospital General de Asturias,  
Oviedo, Spain.

SOURCE: American journal of clinical oncology : official  
publication of the American Radium Society, (2003 Apr) 26  
(2) 107-11.

Journal code: 8207754. ISSN: 0277-3732.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE I)  
(CLINICAL TRIAL, PHASE II)  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200305

ENTRY DATE: Entered STN: 20030426

Last Updated on STN: 20030507

Entered Medline: 20030506

## ABSTRACT:

Because no consensus exists regarding recommendable dose levels for \*\*\*irinotecan\*\*\*, an inpatient dose escalation phase I-II study was initiated in previously treated patients with colorectal cancer. Survival was a secondary endpoint. Thirty-five consecutive patients with progressive disease after 5-fluorouracil-based chemotherapy were enrolled to receive \*\*\*irinotecan\*\*\* starting from 250 mg/m<sup>2</sup>/3 weeks and rising to currently used therapeutic doses. In total, 162 cycles were administered. The median tolerable dose was 250 mg/m<sup>2</sup>. Twelve patients (34%) were unable to tolerate doses greater than 250 mg/m<sup>2</sup>, 10 patients (28%) presented toxicity at 250 mg/m<sup>2</sup> and 2 patients tolerated only 200 mg/m<sup>2</sup>. Three patients (9%) had partial response. The major adverse reactions were grade III-IV diarrhea, grade II-III nausea/vomiting, grade II-III neutropenia, and grade II-III anaemia in 28%, 48%, 11%, and 17% of the patients, respectively. Median survival time and time to progression were 8 and 3 months, respectively. The current \*\*\*irinotecan\*\*\* dose of 350 mg/m<sup>2</sup>/3 weeks appears unacceptably toxic and, hence, a lower dose needs to be considered. The response rates obtained are similar to the results observed in phase III studies, and its activity appears not to be adversely affected with this treatment scheme.

CONTROLLED TERM: Check Tags: Female; Human; Male

Adult

Aged

\*Antineoplastic Agents: AD, administration & dosage

Antineoplastic Agents: TU, therapeutic use

\*Camptothecin: AD, administration & dosage

\*Camptothecin: AA, analogs & derivatives

Camptothecin: TU, therapeutic use

Chemotherapy, Adjuvant

\*Colorectal Neoplasms: DT, drug therapy

DNA Topoisomerases, Type I: AI, antagonists & inhibitors

Enzyme Inhibitors: AD, administration & dosage

Enzyme Inhibitors: TU, therapeutic use

Fluorouracil: TU, therapeutic use

Maximum Tolerated Dose

Middle Aged

Palliative Care

Survival Analysis

Treatment Failure

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 51-21-8 (Fluorouracil);  
7689-03-4 (Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); EC  
5.99.1.2 (DNA Topoisomerases, Type I)

L124 ANSWER 12 OF 25

MEDLINE on STN

ACCESSION NUMBER: 2003153647 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12669404

TITLE: A case of metastatic liver tumor of colorectal cancer  
responding to low-dose CPT-11  
chemotherapy.

AUTHOR: Funahashi Kimihiko; Miki Toshitsugu; Koike Junichi;  
Washizawa Naohiro; Shibata Yumiko; Matsumoto Hiroshi;  
Tokuyama Takayuki; Ryu Masamine; Shiokawa Hiroyuki; Goto  
Tomohiko; Teramoto Tatsuo

CORPORATE SOURCE: First Dept. of Surgery, Toho University School of Medicine.  
SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2003 Mar) 30  
(3) 419-21.

Journal code: 7810034. ISSN: 0385-0684.

PUB. COUNTRY: Japan

DOCUMENT TYPE: (CASE REPORTS)

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: Japanese

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200304  
ENTRY DATE: Entered STN: 20030403  
Last Updated on STN: 20030409  
Entered Medline: 20030408

## ABSTRACT:

We report a case in which low-dose CPT-11 chemotherapy was effective for metastatic liver tumor of sigmoid colon cancer. A 49-year-old male with metastatic liver tumor, who had undergone sigmoidectomy with D2 lymphadenectomy, was treated by low-dose CPT-11 chemotherapy (CPT-11 30 mg/m<sup>2</sup> x 3 days, every 2 weeks). After 7 courses of this chemotherapy, CT and ultrasound examinations showed a reduction of tumor size in the liver. This chemotherapy also showed no high grade toxicities. Therefore, low-dose CPT-11 chemotherapy seems to be effective for metastatic colorectal cancer, and safe in view of toxicities.

CONTROLLED TERM: Check Tags: Human; Male  
\*Adenocarcinoma: DT, drug therapy  
Adenocarcinoma: SC, secondary  
\*Antineoplastic Agents, Phytogenic: AD, administration & dosage  
\*Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
\*Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: SC, secondary  
Dose-Response Relationship, Drug  
Drug Administration Schedule  
English Abstract  
\*Liver Neoplasms: DT, drug therapy  
Liver Neoplasms: SC, secondary  
Middle Aged  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 7689-03-4  
(Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic)

L124 ANSWER 13 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2003098806 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12610870  
TITLE: Optimal dosing schedule in combination therapy  
with irinotecan and doxifluridine in a human  
colorectal cancer xenograft model.  
AUTHOR: Yanagisawa Mieko; Ishikawa Tohru; Ouchi Kaori F; Tanaka  
Yutaka  
CORPORATE SOURCE: Dept. of Product Research, Nippon Roche Research Center.  
SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2003 Feb) 30  
(2) 223-30.  
Journal code: 7810034. ISSN: 0385-0684.  
PUB. COUNTRY: Japan  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: Japanese  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200303  
ENTRY DATE: Entered STN: 20030304  
Last Updated on STN: 20030311  
Entered Medline: 20030310

## ABSTRACT:

A combination therapy with CPT-11 and 5-FU/LV has been recently established as a first-line therapy for metastatic colorectal cancer. However, severe adverse effects have also been reported from this combination therapy, and a modality to reduce the adverse effects is desired. 5'-DFUR, a pro-drug of 5-FU, shows less myelotoxicity than 5-FU, and thus it may be a better partner to combine with CPT-11. However, since each drug has the possibility of inducing diarrhea, there is concern about their use

in combination therapy. Therefore, in the present study, our aim was to establish an optimal schedule in murine models, which shows no increase in diarrhea but maintains potent antitumor activity. In non-tumor bearing mice, \*\*\*CPT\*\*\* -11 was given i.v. at 100 mg/kg/day q2d x 3, and 5'-DFUR was given p.o. at 172 mg/kg/day daily for 14 days. Each of these doses caused diarrhea in the single treatment. CPT-11 was administered simultaneously or sequentially with 5'-DFUR. With the simultaneously administered schedule, the diarrhea appeared stronger than that found in the \*\*\*CPT\*\*\* -11 single or in the 5'-DFUR single treatment groups. On the other hand, with the sequentially administered schedule the diarrhea was not much stronger than that found in the single agent treatment groups. When \*\*\*CPT\*\*\* -11 and 5'-DFUR administrations were separated by three-day intervals, the diarrhea was not augmented at all. In mice bearing human colorectal cancer COLO 205, the antitumor activity of CPT-11 in the combination with 5'-DFUR was additive in all of the examined schedules. The efficacy in the sequential schedule was the same as in the simultaneous schedule. These results suggest that a sequential administration schedule of CPT-11 and 5'-DFUR would be more tolerable than and equally efficacious to the simultaneous administration schedule. Clinical study of this sequential administration in combination therapy is warranted.

CONTROLLED TERM: Check Tags: Human; Male

Animals

\*Antimetabolites, Antineoplastic: AD, administration & dosage

Antimetabolites, Antineoplastic: AE, adverse effects

\*Antineoplastic Agents, Phytogenic: AD, administration & dosage

Antineoplastic Agents, Phytogenic: AE, adverse effects

\*Camptothecin: AD, administration & dosage

Camptothecin: AE, adverse effects

\*Camptothecin: AA, analogs & derivatives

\*Colorectal Neoplasms: DT, drug therapy

Dose-Response Relationship, Drug

Drug Administration Schedule

English Abstract

\*Floxuridine: AD, administration & dosage

Floxuridine: AE, adverse effects

Mice

Mice, Inbred BALB C

Mice, Nude

Neoplasm Transplantation

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 3094-09-5  
(5'-deoxy-5-fluorouridine); 50-91-9 (Floxuridine);  
7689-03-4 (Camptothecin)

CHEMICAL NAME: 0 (Antimetabolites, Antineoplastic); 0 (Antineoplastic  
Agents, Phytogenic)

L124 ANSWER 14 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2003097320 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12610178

TITLE: Phase III comparison of two irinotecan  
dosing regimens in second-line therapy of  
metastatic colorectal cancer.

AUTHOR: Fuchs Charles S; Moore Melvin R; Harker Graydon; Villa  
Luis; Rinaldi David; Hecht J Randolph

CORPORATE SOURCE: Dana-Farber Cancer Institute, Boston, MA 02115, USA..  
charles\_fuchs@dfci.harvard.edu

SOURCE: Journal of clinical oncology : official journal of the  
American Society of Clinical Oncology, (2003 Mar 1) 21 (5)  
807-14.

Journal code: 8309333. ISSN: 0732-183X.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE III)  
Journal; Article; (JOURNAL ARTICLE)  
(MULTICENTER STUDY)  
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200303  
ENTRY DATE: Entered STN: 20030302  
Last Updated on STN: 20030331  
Entered Medline: 20030328

## ABSTRACT:

**PURPOSE:** Randomized trials in fluorouracil (FU)-refractory colorectal cancer demonstrate significant survival advantages for patients receiving \*\*\*irinotecan\*\*\*. We prospectively compared the efficacy and tolerability of two irinotecan regimens (once a week for 4 weeks followed by a 2-week rest period [weekly] v once every 3 weeks) in such patients. **PATIENTS AND METHODS:** This multicenter, open-label, phase III study randomly assigned patients in a 1:2 ratio to irinotecan given either weekly (125 mg/m<sup>2</sup>) or once every 3 weeks (350 mg/m<sup>2</sup>, or 300 mg/m<sup>2</sup> in patients who were  $\geq$  70 years of age, who had Eastern Cooperative Oncology Group performance status equal to 2, or who had prior pelvic irradiation). **RESULTS:** With median follow-up of 15.8 months, there was no significant difference in 1-year survival (46% v 41%, respectively;  $P = .42$ ), median survival (9.9 v 9.9 months, respectively;  $P = .43$ ), or median time to progression (4.0 v 3.0 months, respectively;  $P = .54$ ) between the two regimens. Grade 3/4 diarrhea occurred in 36% of patients treated weekly and in 19% of those treated once every 3 weeks ( $P = .002$ ). Grade 3/4 neutropenia occurred in 29% of patients treated weekly and 34% of those treated once every 3 weeks ( $P = .35$ ). Treatment-related mortality occurred in five patients (5.3%) receiving irinotecan weekly and three patients (1.6%) given therapy once every 3 weeks ( $P = .12$ ). Global quality of life was not statistically different between treatment groups. **CONCLUSION:** Irinotecan schedules of weekly and of once every 3 weeks demonstrated similar efficacy and quality of life in patients with FU-refractory, metastatic colorectal cancer. The regimen of once every 3 weeks was associated with a significantly lower incidence of severe diarrhea.

**CONTROLLED TERM:** Check Tags: Comparative Study; Female; Human; Male; Support, Non-U.S. Gov't  
\*Adenocarcinoma: DT, drug therapy  
Adenocarcinoma: MO, mortality  
Adenocarcinoma: SC, secondary  
Aged  
\*Antineoplastic Agents, Phytogenic: AD, administration & dosage  
Antineoplastic Agents, Phytogenic: TU, therapeutic use  
Bilirubin: ME, metabolism  
\*Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Camptothecin: TU, therapeutic use  
\*Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: MO, mortality  
Colorectal Neoplasms: PA, pathology  
\*DNA Topoisomerases, Type I: AI, antagonists & inhibitors  
Disease Progression  
\*Liver Neoplasms: DT, drug therapy  
Liver Neoplasms: MO, mortality  
Liver Neoplasms: SC, secondary  
\*Lung Neoplasms: DT, drug therapy  
Lung Neoplasms: MO, mortality  
Lung Neoplasms: SC, secondary  
Prospective Studies  
Quality of Life



Salvage Therapy  
Survival Rate  
Treatment Outcome  
Tumor Markers, Biological: AN, analysis

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 635-65-4 (Bilirubin);  
7689-03-4 (Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic); 0 (Tumor Markers,  
Biological); EC 5.99.1.2 (DNA Topoisomerases, Type I)

L124 ANSWER 15 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2002694653 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12450427

TITLE: Irinotecan plus oxaliplatin: a promising  
combination for advanced colorectal cancer.

AUTHOR: Wasserman E; Sutherland W; Cvitkovic E

CORPORATE SOURCE: Cvitkovic & Associates Consultants, Argentina, Echeverria  
1442, E.P. of 49 (1428), Buenos Aires, Argentina..  
e\_wasserman@ciudad.com.ar

SOURCE: Clinical colorectal cancer, (2001 Nov) 1 (3) 149-53. Ref:  
24  
Journal code: 101120693. ISSN: 1533-0028.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200301

ENTRY DATE: Entered STN: 20021214  
Last Updated on STN: 20030129  
Entered Medline: 20030128

## ABSTRACT:

The standard treatment for advanced colorectal cancer (CRC) has been 5-fluorouracil (5-FU)-based chemotherapy. However, addition of \*\*\*irinotecan\*\*\*, a topoisomerase I inhibitor, to the combination of 5-FU and leucovorin (LV) has proven to be superior to treatment with 5-FU/LV alone in both chemo-naïve as well as previously treated patients. Oxaliplatin, a 1,2-diaminocyclohexane platinum compound, in combination with 5-FU and LV, has demonstrated superiority as first-line therapy over 5-FU and LV in terms of response rate and time to progression. The irinotecan/oxaliplatin combination showed synergistic activity in vitro, and the optimal dose safety profile has been explored in several phase I studies. Neutropenia and diarrhea were the dose-limiting toxicities. The recommended dose of irinotecan/oxaliplatin in every-2-week and every-3-week schedules ranged from 150-200 mg/m<sup>2</sup> and 85 mg/m<sup>2</sup>, respectively. In the weekly schedule, the recommended doses of irinotecan/oxaliplatin were 65 mg/m<sup>2</sup> and 60 mg/m<sup>2</sup>. Promising clinical efficacy in CRC was observed in all studies. A recent randomized phase II study revealed that the irinotecan/oxaliplatin combination has equivalent clinical activity to other 5-FU-based combinations and a manageable toxicity profile. The evaluation of irinotecan/oxaliplatin in phase III trials as well as in combination with 5-FU is ongoing.

CONTROLLED TERM: Check Tags: Human  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Clinical Trials  
\*Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: PA, pathology  
Drug Administration Schedule  
Drug Synergism

Neoplasm Staging  
Organoplatinum Compounds: AD, administration & dosage  
Treatment Outcome

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 63121-00-6  
(oxaliplatin); 7689-03-4 (Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0  
(Organoplatinum Compounds)

L124 ANSWER 16 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2002694472 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12445376

TITLE: Advances in the treatment of metastatic colorectal cancer.

AUTHOR: Fishman A D; Wadler S

CORPORATE SOURCE: Department of Oncology, Montefiore Medical Center, Albert  
Einstein College of Medicine, Bronx, NY, USA.

SOURCE: Clinical colorectal cancer, (2001 May) 1 (1) 20-35. Ref:  
122  
Journal code: 101120693. ISSN: 1533-0028.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200212

ENTRY DATE: Entered STN: 20021214  
Last Updated on STN: 20021220  
Entered Medline: 20021219

## ABSTRACT:

Colorectal cancer represents the third leading cause of cancer mortality in the United States. During the past four decades, 5-fluorouracil (5-FU) has served as the cornerstone of therapy for individuals with advanced colorectal cancer (ACRC). Despite numerous attempts at maximizing efficacy of 5-FU through biochemical modulation, a significant benefit in terms of survival has never been realized. The recent emergence of novel chemotherapeutic drugs employing different mechanisms of action than 5-FU has led to the incorporation of \*\*\*irinotecan\*\*\* (CPT-11) with 5-FU/leucovorin as the new standard first-line regimen for future trials. This review outlines emerging data utilizing oral fluoropyrimidines and other new agents including oxaliplatin, raltitrexed, and eniluracil. Randomized clinical trials are currently underway in an effort to define optimal combination chemotherapy regimens, scheduling of agents, duration of therapy, and choice of therapy using a variety of prognostic molecular markers.

CONTROLLED TERM: Check Tags: Human  
Administration, Oral  
Antibodies, Monoclonal: AD, administration & dosage  
\*Antineoplastic Agents: AD, administration & dosage  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Cancer Vaccines: AD, administration & dosage  
\*Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: PA, pathology  
Deoxycytidine: AD, administration & dosage  
\*Deoxycytidine: AA, analogs & derivatives  
Drug Administration Schedule  
Fluorouracil: AD, administration & dosage  
Liver Neoplasms: SC, secondary  
Liver Neoplasms: TH, therapy  
Neoplasm Metastasis  
Organoplatinum Compounds: AD, administration & dosage  
Prodrugs: AD, administration & dosage  
Quinazolines: AD, administration & dosage

Randomized Controlled Trials  
Thiophenes: AD, administration & dosage  
Uracil: AD, administration & dosage  
\*Uracil: AA, analogs & derivatives

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 112887-68-0  
(raltitrexed); 154361-50-9 (capecitabine); 51-21-8  
(Fluorouracil); 59989-18-3 (5-ethynyluracil); 63121-00-6  
(oxaliplatin); 66-22-8 (Uracil); 7689-03-4 (Camptothecin);  
951-77-9 (Deoxycytidine)

CHEMICAL NAME: 0 (Antibodies, Monoclonal); 0 (Antineoplastic Agents); 0  
(Cancer Vaccines); 0 (Organoplatinum Compounds); 0  
(Prodrugs); 0 (Quinazolines); 0 (Thiophenes)

L124 ANSWER 17 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2002066352 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11793596  
TITLE: [Chemotherapy of colorectal carcinoma].  
Chemotherapie des Kolonkarzinoms.  
COMMENT: Erratum in: Internist (Berl) 2002 Mar;43(3):409  
AUTHOR: Lutz M P; Adler G  
CORPORATE SOURCE: Abteilung Innere Medizin I, Medizinische Universitätsklinik  
und Poliklinik, Universitätsklinikum, Robert-Koch-Strasse  
8, 89070 Ulm.  
SOURCE: Der Internist, (2001 Dec) 42 (12) 1567-8, 1571-6, 1578-82.  
Ref: 63  
Journal code: 0264620. ISSN: 0020-9554.  
PUB. COUNTRY: Germany: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: German  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200202  
ENTRY DATE: Entered STN: 20020125  
Last Updated on STN: 20020720  
Entered Medline: 20020208

CONTROLLED TERM: Check Tags: Human  
Administration, Oral  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
\*Carcinoma: DT, drug therapy  
Chemotherapy, Adjuvant  
Clinical Trials  
\*Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: MO, mortality  
Drug Administration Schedule  
Fluorouracil: AD, administration & dosage  
Folic Acid: AD, administration & dosage  
Neoadjuvant Therapy  
Organoplatinum Compounds: AD, administration & dosage  
Palliative Care  
Survival Analysis  
Treatment Outcome

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 51-21-8 (Fluorouracil);  
59-30-3 (Folic Acid); 63121-00-6 (oxaliplatin); 7689-03-4  
(Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0  
(Organoplatinum Compounds)

L124 ANSWER 18 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2001288918 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11340371  
TITLE: A dose-finding study of irinotecan (CPT-11) plus a four-day continuous 5-fluorouracil infusion in advanced colorectal cancer.  
AUTHOR: Kakolyris S; Souglakos J; Kouroussis C; Androulakis N; Mavroudis D; Kalbakis K; Kotsakis A; Vardakis N; Koukourakis M; Romanos J; Georgoulis V  
CORPORATE SOURCE: Department of Medical Oncology, School of Medicine, University General Hospital of Heraklion, Heraklion, Crete, Greece.  
SOURCE: Oncology, (2001) 60 (3) 207-13.  
Journal code: 0135054. ISSN: 0030-2414.  
PUB. COUNTRY: Switzerland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200105  
ENTRY DATE: Entered STN: 20010529  
Last Updated on STN: 20010529  
Entered Medline: 20010524

## ABSTRACT:

**OBJECTIVE:** Irinotecan (CPT-11) has shown considerable activity in colorectal cancer, and its combination with 5-fluorouracil (5-FU) represents an attractive approach. A phase I study was conducted to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs) of CPT-11 in combination with a continuous infusion of 5-FU for 4 days. **METHODS:** Forty-two patients with histologically confirmed metastatic colorectal cancer who had not received prior treatment for advanced disease were enrolled. The patients' median age was 64 years; 26 (62%) patients were men, and the performance status (WHO) was 0 in 26 (62%) patients, 1 in 15 (36%) and 2 in 1 (2%). Twenty-two (52%) patients had 2 or more metastatic sites. **CPT-11** (starting dose 200 mg/m<sup>2</sup>) was administered as a 30-min intravenous infusion with increments of 50 mg/m<sup>2</sup> on day 4. 5-FU (starting dose 400 mg/m<sup>2</sup>) was administered as a 4-day continuous intravenous infusion with increments of 50 mg/m<sup>2</sup> on days 1-4. Treatment was repeated every 4 weeks. **RESULTS:** The MTD of the combination was found to be 600 mg/m<sup>2</sup> for 5-FU and 350 mg/m<sup>2</sup> for \*\*\*CPT\*\*\* -11. Neutropenia, febrile neutropenia and delayed diarrhea were the DLTs. Grade 3/4 neutropenia was observed in 22 (13%) out of 169 administered treatment cycles, febrile neutropenia in 7 (4%) and grade 3/4 diarrhea in 20 (12%). Other toxicities were mild. Among 36 patients evaluable for response, partial response was achieved in 8 (22%), stable disease in 12 (33%) and progressive disease in 16 (44%) patients. Responses were mostly seen at the higher dose levels. **CONCLUSIONS:** The combination of a 4-day continuous infusion of 5-FU followed by CPT-11 represents an active and well-tolerated regimen for patients with colorectal cancer. This regimen merits further evaluation in phase II studies.

Copyright 2001 S. Karger AG, Basel

**CONTROLLED TERM:** Check Tags: Female; Human; Male; Support, Non-U.S. Gov't  
Adult  
Aged  
\*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use  
\*Camptothecin: AD, administration & dosage  
Camptothecin: AE, adverse effects  
\*Camptothecin: AA, analogs & derivatives  
\*Colorectal Neoplasms: DT, drug therapy  
\*Fluorouracil: AD, administration & dosage  
Fluorouracil: AE, adverse effects  
Infusions, Intravenous  
Middle Aged

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 51-21-8 (Fluorouracil);  
7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols)

L124 ANSWER 19 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2001180888 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11161230  
TITLE: **Irinotecan (CPT-11): recent**  
developments and future directions--colorectal cancer and  
beyond.  
COMMENT: Comment in: Oncologist. 2001;6(1):65. PubMed ID: 11161229  
AUTHOR: Rothenberg M L  
CORPORATE SOURCE: Division of Hematology/Oncology, Vanderbilt University  
Medical Center, Nashville, Tennessee 37232-5536, USA..  
mace.rothenberg@mcmmail.vanderbilt.edu  
SOURCE: oncologist, (2001) 6 (1) 66-80. Ref: 99  
Journal code: 9607837. ISSN: 1083-7159.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200103  
ENTRY DATE: Entered STN: 20010404  
Last Updated on STN: 20010404  
Entered Medline: 20010329

## ABSTRACT:

Since its approval in the United States in 1996, **irinotecan** (  
\*\*\*CPT\*\*\* -11, **Camptosar**, Pharmacia Corp.; Peapack, NJ)  
has undergone extensive clinical evaluation. In the past five years, the focus  
of development has evolved from evaluation of single-agent activity in  
refractory disease settings to evaluation of front-line **irinotecan**  
-based combination chemotherapy regimens and integration of **irinotecan**  
into combined modality regimens. Important studies have been performed  
clarifying the role of **irinotecan** in treating colorectal and other  
gastrointestinal cancers, small cell and non-small cell lung cancer, and a  
variety of other malignancies. Preclinical studies performed in conjunction  
with these clinical trials have also provided significant insights into the  
pharmacology, metabolism, mechanisms of resistance, and molecular determinants  
of response. This review summarizes that progress, focusing on the  
achievements of the past five years.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't  
Antineoplastic Agents, Phytogenic: AD, administration &  
dosage  
\*Antineoplastic Agents, Phytogenic: PD, pharmacology  
**Camptothecin: AD, administration & dosage**  
**\*Camptothecin: AA, analogs & derivatives**  
\*Camptothecin: PD, pharmacology  
Clinical Trials  
**\*Colorectal Neoplasms: DT, drug therapy**  
Combined Modality Therapy  
**Drug Administration Schedule**  
Drug Therapy, Combination  
\*Gastrointestinal Neoplasms: DT, drug therapy  
\*Lung Neoplasms: DT, drug therapy  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 7689-03-4  
(Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic)

L124 ANSWER 20 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2001080177 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11142161  
TITLE: Progress in chemotherapy for colorectal cancer.  
AUTHOR: Sasaki T; Maeda Y  
CORPORATE SOURCE: Department of Chemotherapy, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan.  
SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2000 Dec) 27 (14) 2185-92. Ref: 36  
Journal code: 7810034. ISSN: 0385-0684.  
PUB. COUNTRY: Japan  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: Japanese  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200101  
ENTRY DATE: Entered STN: 20010322  
Last Updated on STN: 20010322  
Entered Medline: 20010111

## ABSTRACT:

Among colorectal cancer patients with recurrent or metastatic sites, survival was significantly prolonged for a group undergoing LV/5-FU therapy based on biochemical modulation compared with a group receiving no chemotherapy (best supportive care). LV/5-FU combination therapy is recognized as the standard therapy for colorectal cancer, but recently LV/5-FU plus oxaliplatin and LV/5-FU plus CPT-11 have appeared to be more effective than LV/5-FU in some randomized studies. Capecitabine, UFT/LV and S-1 are new oral drugs that are at least comparable to LV/5-FU in antitumor activity, but superior in tolerability, which benefits the patients' quality of life, especially elderly patients with colorectal cancer. Clinical combination studies using CDDP or CPT-11 with these oral drugs are now being performed. Much is expected of these drugs.

CONTROLLED TERM: Check Tags: Human  
\*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Cisplatin: AD, administration & dosage  
Clinical Trials  
\*Colorectal Neoplasms: DT, drug therapy  
Deoxycytidine: AD, administration & dosage  
Deoxycytidine: AA, analogs & derivatives  
Drug Administration Schedule  
Drug Combinations  
English Abstract  
Fluorouracil: AD, administration & dosage  
Leucovorin: AD, administration & dosage  
Oxonic Acid: AD, administration & dosage  
Pyridines: AD, administration & dosage  
Tegafur: AD, administration & dosage  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 150863-82-4 (S 1 (combination)); 154361-50-9 (capecitabine); 15663-27-1 (Cisplatin); 17902-23-7 (Tegafur); 51-21-8 (Fluorouracil); 58-05-9 (Leucovorin); 7689-03-4 (Camptothecin); 937-13-3 (Oxonic Acid); 951-77-9 (Deoxycytidine)  
CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Drug Combinations); 0 (Pyridines)

L124 ANSWER 21 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2000424148 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10945022  
TITLE: State of the treatment for gastrointestinal cancer.

AUTHOR: Baba H; Kohnoe S; Endo K; Ikeda Y; Toh Y; Nakashima H;  
Okamura T  
CORPORATE SOURCE: Dept. of Gastroenterologic Surgery, National Kyushu Cancer  
Center.  
SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2000 Jul) 27  
(8) 1233-46. Ref: 23  
Journal code: 7810034. ISSN: 0385-0684.  
PUB. COUNTRY: Japan  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
LANGUAGE: Japanese  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200009  
ENTRY DATE: Entered STN: 20000915  
Last Updated on STN: 20000915  
Entered Medline: 20000906

## ABSTRACT:

We reviewed the results of chemotherapy for gastrointestinal cancer. In Western countries, FAMTX or ECF is recognized as the standard therapy for gastric cancer. In Japan, no standard chemotherapeutic regimen has been established yet, but FP or MTX/5-FU are often used as a first line chemotherapy. There have been only a few clinical trials of adjuvant chemotherapy for gastric cancer in which this regimen was identified as having a statistically significant effect. For colon cancer, 5-FU plus LV are now used as the standard therapy. Recently, however, it has been shown that 5-FU + LV combined with CPT-11 is more active than 5-FU + LV alone. The efficacy of oral anticancer agents such as UFT + LV, S-1, and capecitabine have also been shown to be equally or more active than i.v. administration of 5-FU and LV, so that the standard therapy for colon cancer will be changed in near future.

CONTROLLED TERM: Check Tags: Human  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
**Camptothecin: AD, administration & dosage**  
**\*Camptothecin: AA, analogs & derivatives**  
Cisplatin: AD, administration & dosage  
Clinical Trials, Phase II  
**\*Colorectal Neoplasms: DT, drug therapy**  
Doxorubicin: AD, administration & dosage  
**Drug Administration Schedule**  
English Abstract  
Fluorouracil: AD, administration & dosage  
Mitomycin: AD, administration & dosage  
\*Stomach Neoplasms: DT, drug therapy  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 15663-27-1 (Cisplatin);  
23214-92-8 (Doxorubicin); 50-07-7 (Mitomycin); 51-21-8  
(Fluorouracil); 7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (FAM  
protocol)

L124 ANSWER 22 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2000423498 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10969617  
TITLE: [New options in patients with metastatic cancer of the  
colon already treated: platinum salts].  
Nuove opzioni in pazienti già trattati con cancro del colon  
metastatico: i sali del platino.  
AUTHOR: Carlei G  
CORPORATE SOURCE: Divisione di Oncologia Medica B, Centro di Riferimento  
Oncologico, Aviano.. gcarlei@ets.it  
SOURCE: Tumori, (2000 May-Jun) 86 (3 Suppl) S42-8. Ref: 58

Journal code: 0111356. ISSN: 0300-8916.

PUB. COUNTRY: Italy  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW LITERATURE)

LANGUAGE: Italian  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200009  
ENTRY DATE: Entered STN: 20000915  
Last Updated on STN: 20000915  
Entered Medline: 20000907

CONTROLLED TERM: Check Tags: Human  
Antineoplastic Combined Chemotherapy Protocols: AE,  
adverse effects  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Chronotherapy  
Cisplatin: AD, administration & dosage  
Cisplatin: AE, adverse effects  
\*Colonic Neoplasms: DT, drug therapy  
Colonic Neoplasms: PA, pathology  
Cyclophosphamide: AD, administration & dosage  
Cyclophosphamide: AE, adverse effects  
DNA Repair  
Drug Administration Schedule  
Drug Resistance, Multiple  
Drug Synergism  
Fluorouracil: AD, administration & dosage  
Fluorouracil: AE, adverse effects  
Organoplatinum Compounds: AD, administration & dosage  
Organoplatinum Compounds: AE, adverse effects  
Survival Analysis

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 15663-27-1 (Cisplatin);  
50-18-0 (Cyclophosphamide); 51-21-8 (Fluorouracil);  
63121-00-6 (oxaliplatin); 7689-03-4 (Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0  
(Organoplatinum Compounds)

L124 ANSWER 23 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 2000234614 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10774581  
TITLE: [CPT-11: new drug for metastatic  
colorectal cancer].  
CPT-11: farmaco originale per il cancro  
colorettale metastatico.

AUTHOR: Barone C; Pozzo C; Cassano A  
CORPORATE SOURCE: Oncologia Medica, Universita Cattolica del Sacro Cuore,  
Roma.

SOURCE: Tumori, (1999 Nov-Dec) 85 (6) A1-11. Ref: 34  
Journal code: 0111356. ISSN: 0300-8916.

PUB. COUNTRY: Italy  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LANGUAGE: Italian  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200005  
ENTRY DATE: Entered STN: 20000518  
Last Updated on STN: 20000518  
Entered Medline: 20000511



CONTROLLED TERM: Check Tags: Human  
Antineoplastic Agents, Phytogenic: AD, administration & dosage  
Antineoplastic Agents, Phytogenic: AE, adverse effects  
Antineoplastic Agents, Phytogenic: PK, pharmacokinetics  
\*Antineoplastic Agents, Phytogenic: PD, pharmacology  
\*Antineoplastic Agents, Phytogenic: TU, therapeutic use  
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use  
    **Camptothecin: AD, administration & dosage**  
    Camptothecin: AE, adverse effects  
    **\*Camptothecin: AA, analogs & derivatives**  
    Camptothecin: PK, pharmacokinetics  
    Camptothecin: PD, pharmacology  
    Camptothecin: TU, therapeutic use  
    Clinical Trials, Phase I  
    Clinical Trials, Phase II  
    **\*Colorectal Neoplasms: DT, drug therapy**  
\*Colorectal Neoplasms: SC, secondary  
    **Drug Administration Schedule**  
    Randomized Controlled Trials  
    Survival Analysis  
    Treatment Outcome  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic); 0 (Antineoplastic Combined Chemotherapy Protocols)

L124 ANSWER 24 OF 25 MEDLINE on STN  
ACCESSION NUMBER: 97373288 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9229329  
TITLE: CPT-11: the European clinical development.  
AUTHOR: Terret C; Couteau C; Armand J P  
CORPORATE SOURCE: Institut Gustave Roussy, Villejuif, France.  
SOURCE: Journal of infusional chemotherapy, (1996 Summer) 6 (3) 152-7. Ref: 44  
Journal code: 9306406. ISSN: 1060-0051.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
    **General Review; (REVIEW)**  
    (REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199709  
ENTRY DATE: Entered STN: 19970922  
Last Updated on STN: 19970922  
Entered Medline: 19970909

## ABSTRACT:

CPT-11 is a camptothecin derivative with a broad spectrum of antitumor activity, both in vitro and in vivo. Like camptothecin, \*\*\*CPT\*\*\* -11 is a selective DNA topoisomerase I inhibitor. Phase I trials were conducted in Europe to determine the dose and schedule for phase II trials. These phase I trials assessed the toxicity of CPT-11 in 235 patients and tested three administration schedules: a single infusion once every 3 weeks; a weekly infusion for 3 out of 4 weeks; and a daily infusion for 3 consecutive days every 3 weeks. The maximum tolerated dose (MTD) was 115 mg/m<sup>2</sup> in the daily schedule and 145 mg/m<sup>2</sup> in the weekly schedule. When the drug was administered once every 3 weeks, diarrhea became the dose-limiting toxicity at doses above 350 mg/m<sup>2</sup>. This schedule offered the highest dose intensity and the best tolerability profile, and was the most convenient for outpatient treatment. Finally, using this schedule, concomitant

administration of high-dose loperamide allowed the dose of CPT-\*\*\*11\*\*\* to be increased to 750 mg/m<sup>2</sup>. An ongoing phase I trial is investigating the combination of CPT-11 and 5-fluorouracil (5-FU) in various solid tumors. Although the MTD has not yet been reached, preliminary results show no pharmacokinetic interaction between the two drugs, contrary to a previous Japanese study. Based on the results of the three phase I trials, CPT-11 350 mg/m<sup>2</sup> as an intravenous infusion over 30 minutes once every 3 weeks was recommended for phase II trials, which started in Europe in 1992. To date, CPT-11 has shown remarkable efficacy in colorectal cancer, even in patients resistant to 5-FU. Interesting results have also been obtained in pancreatic, cervical and lung cancers. Future trials will explore the place of CPT-11 in combination with other cytotoxic agents or radiotherapy.

CONTROLLED TERM: Check Tags: Female; Human  
 Antineoplastic Agents, Phytogenic: PK, pharmacokinetics  
 \*Antineoplastic Agents, Phytogenic: TU, therapeutic use  
 Breast Neoplasms: DT, drug therapy  
 \*Camptothecin: AA, analogs & derivatives  
 Camptothecin: PK, pharmacokinetics  
 Camptothecin: TU, therapeutic use  
 Cervix Neoplasms: DT, drug therapy  
 Clinical Trials, Phase I  
 Clinical Trials, Phase II  
 \*Colorectal Neoplasms: DT, drug therapy  
 Dose-Response Relationship, Drug  
 Drug Administration Schedule  
 Europe  
 Lung Neoplasms: DT, drug therapy  
 \*Pancreatic Neoplasms: DT, drug therapy  
 CAS REGISTRY NO.: 100286-90-6 (irinotecan); 7689-03-4  
 (Camptothecin)  
 CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic)

L124 ANSWER 25 OF 25 MEDLINE on STN  
 ACCESSION NUMBER: 97046549 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8891470  
 TITLE: Irinotecan. A review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer.  
 AUTHOR: Wiseman L R; Markham A  
 CORPORATE SOURCE: Adis International Limited, Auckland, New Zealand.  
 SOURCE: Drugs, (1996 Oct) 52 (4) 606-23. Ref: 66  
 Journal code: 7600076. ISSN: 0012-6667.  
 PUB. COUNTRY: New Zealand  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199701  
 ENTRY DATE: Entered STN: 19970219  
 Last Updated on STN: 19980206  
 Entered Medline: 19970130

## ABSTRACT:

Irinotecan (CPT-II) is a semisynthetic derivative of camptothecin. It and other camptothecin analogues/derivatives appear to exert their antitumour activity by binding to topoisomerase I. The active metabolite of \*\*\*irinotecan\*\*\*, 7-ethyl-10-hydroxycamptothecin (SN-38), has demonstrated potent growth inhibition of human colorectal cancer cells in vitro, with superior activity to fluorouracil. In phase II clinical studies in patients with advanced colorectal cancer, objective response rates after \*\*\*irinotecan\*\*\* therapy ranged between 20.5 and 32%. These studies used a

range of **irinotecan** regimens including 350 mg/m<sup>2</sup> once every 3 weeks (Europe), 125 to 150 mg/m<sup>2</sup> once a week for 4 weeks followed by a 2-week drug-free interval (US) and 100 mg/m<sup>2</sup>/week or 150 mg/m<sup>2</sup> every 2 weeks (Japan). The median duration of response ranged between 5.6 and 10.6 months. Disease stabilisation occurred in 30 to 71.2% of patients. Objective response rates to \*\*\*irinotecan\*\*\* therapy in patients who had received no prior chemotherapy were similar to those in patients pretreated with fluorouracil. Importantly, \*\*\*irinotecan\*\*\* also induced responses in some patients with tumours refractory to fluorouracil. Severe (grade 3 or 4) neutropenia and diarrhoea, which occurred in up to 40% of patients receiving **irinotecan** therapy in phase II studies, require careful monitoring and appropriate management. Thus, **irinotecan** is a valuable agent for the second-line treatment of patients with advanced colorectal cancer who fail to respond to or relapse after fluorouracil therapy.

CONTROLLED TERM: Check Tags: Human; In Vitro  
Antineoplastic Agents, Phytogenic: AD, administration & dosage  
Antineoplastic Agents, Phytogenic: PD, pharmacology  
\*Antineoplastic Agents, Phytogenic: TU, therapeutic use  
Camptothecin: AD, administration & dosage  
\*Camptothecin: AA, analogs & derivatives  
Camptothecin: PK, pharmacokinetics  
Camptothecin: PD, pharmacology  
Camptothecin: TU, therapeutic use  
Clinical Trials, Phase I  
Clinical Trials, Phase II  
\*Colorectal Neoplasms: DT, drug therapy  
Dose-Response Relationship, Drug  
Drug Interactions  
Drug Resistance, Multiple  
Europe  
Japan  
Tissue Distribution  
Treatment Outcome  
United States  
CAS REGISTRY NO.: 100286-90-6 (**irinotecan**); 7689-03-4  
(Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic)

=> fil medl; d que l40; d que l43; s l40 or l43  
 FILE 'MEDLINE' ENTERED AT 13:14:50 ON 20 JUL 2004

FILE LAST UPDATED: 17 JUL 2004 (20040717/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLD MEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L14 77610 SEA FILE=MEDLINE ABB=ON COLORECTAL NEOPLASMS+NT/CT  
 L19 12633 SEA FILE=MEDLINE ABB=ON L14 (L) (DT OR PC)/CT  
 L20 7778 SEA FILE=MEDLINE ABB=ON L19/MAJ  
 L37 2628 SEA FILE=MEDLINE ABB=ON THALIDOMIDE/CT  
 L40 7 SEA FILE=MEDLINE ABB=ON L37 AND L20

L14 77610 SEA FILE=MEDLINE ABB=ON COLORECTAL NEOPLASMS+NT/CT  
 L19 12633 SEA FILE=MEDLINE ABB=ON L14 (L) (DT OR PC)/CT  
 L20 7778 SEA FILE=MEDLINE ABB=ON L19/MAJ  
 L37 2628 SEA FILE=MEDLINE ABB=ON THALIDOMIDE/CT  
 L40 7 SEA FILE=MEDLINE ABB=ON L37 AND L20  
 L41 55065 SEA FILE=MEDLINE ABB=ON ANTINEOPLASTIC COMBINED CHEMOTHERAPY  
 PROTOCOLS/CT  
 L42 16 SEA FILE=MEDLINE ABB=ON L14 AND L37 NOT L41  
 L43 12 SEA FILE=MEDLINE ABB=ON L42 NOT L40

L125 19 L40 OR L43

=> d iall 1-19

L125 ANSWER 1 OF 19 MEDLINE on STN  
 ACCESSION NUMBER: 2003613104 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 14696081  
 TITLE: Molecular epidemiology: new insights into diagnosis and prognosis.  
 AUTHOR: Lang Nicholas P  
 SOURCE: Journal of surgical oncology, (2004 Jan) 85 (1) 4-6.  
 Journal code: 0222643. ISSN: 0022-4790.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Editorial  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200401  
 ENTRY DATE: Entered STN: 20031230  
 Last Updated on STN: 20040130  
 Entered Medline: 20040129  
 CONTROLLED TERM: Check Tags: Female; Human; Male  
 Alleles  
 Angiogenesis Inhibitors: TU, therapeutic use  
 \*Breast Neoplasms: DI, diagnosis

\*Colonic Neoplasms: DI, diagnosis  
\*Epidemiology, Molecular  
Gene Expression  
Glutathione Transferase: GE, genetics  
Isoenzymes: GE, genetics  
Melanoma: DI, diagnosis  
Melanoma: DT, drug therapy  
Organoplatinum Compounds  
Polymorphism (Genetics)  
Prognosis  
Reverse Transcriptase Polymerase Chain Reaction  
Sentinel Lymph Node Biopsy  
Sulfotransferases: GE, genetics  
Thalidomide: TU, therapeutic use  
Tumor Necrosis Factor: GE, genetics  
CAS REGISTRY NO.: 50-35-1 (Thalidomide); 63121-00-6 (oxaliplatin)  
CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Isoenzymes); 0  
(Organoplatinum Compounds); 0 (Tumor Necrosis Factor); EC  
2.5.1.- (glutathione S-transferase pi); EC 2.5.1.18  
(Glutathione Transferase); EC 2.8.2 (Sulfotransferases); EC  
2.8.2.- (SULT1C1 protein, human)

L125 ANSWER 2 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2003561678 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 14649541  
TITLE: Effect of 3-fluorothalidomide and 3-methylthalidomide  
enantiomers on tumor necrosis factor production and  
antitumor responses to the antivasular agent  
5,6-dimethylxanthenone-4-acetic acid (DMXAA).  
AUTHOR: Chung Francisco; Palmer Brian D; Muller George W; Man  
Hon-Wah; Kestell Phillip; Baguley Bruce C; Ching Lai-Ming  
CORPORATE SOURCE: Auckland Cancer Society Research Center, Faculty of Medical  
and Health Sciences, The University of Auckland, Auckland,  
New Zealand.  
SOURCE: Oncology research, (2003) 14 (2) 75-82.  
Journal code: 9208097. ISSN: 0965-0407.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200407  
ENTRY DATE: Entered STN: 20031216  
Last Updated on STN: 20040703  
Entered Medline: 20040702

ABSTRACT: 5,6-Dimethylxanthenone-4-acetic acid (DMXAA) is an antivasular drug that induces tumor necrosis factor (TNF) in mice. Thalidomide inhibits TNF induction by DMXAA and also potentiates its antitumor activity. We investigated whether these effects were enantiomer specific, using the R- or S-enantiomers of two nonracemizable thalidomide analogues. Racemic 3-fluorothalidomide (3FThal) and racemic 3-methylthalidomide (3MeThal) were separated into enantiomers of greater than 98% optical purity using preparative chiral column chromatography. C57Bl/6 mice implanted with subcutaneous Colon 38 tumors were treated with DMXAA (25 mg/kg) alone or together with the pure R- or S-enantiomers by a single i.p. injection. TNF levels in the serum or tumor tissues 3 h after treatment were measured using ELISAs and tumor growth was also measured. 3FThal and 3MeThal, at their respective single maximum tolerated doses (MTD) of 15 and 50 mg/kg, were more toxic in mice than thalidomide (100 mg/kg). The R- and S-enantiomers of either 3FThal or 3MeThal, at their respective MTD, inhibited DMXAA-induced TNF activity in serum and tumor tissue, but no significant differences were observed between the enantiomers. Coadministration of racemic or enantiomers of 3FThal or 3MeThal at their

respective MTD did not potentiate the antitumor responses above that obtained with DMXAA alone, and no enantioselectivity was apparent. We conclude that there is no advantage in using the nonracemizable thalidomide analogues to improve the antitumor activity of DMXAA.

CONTROLLED TERM: Check Tags: Female; Support, Non-U.S. Gov't  
Angiogenesis Inhibitors: AD, administration & dosage  
\*Angiogenesis Inhibitors: TU, therapeutic use  
Animals  
\*Colonic Neoplasms: DT, drug therapy  
Colonic Neoplasms: ME, metabolism  
Drug Synergism  
Enzyme-Linked Immunosorbent Assay  
Injections, Intraperitoneal  
Maximum Tolerated Dose  
Mice  
Mice, Inbred C57BL  
Molecular Structure  
Neoplasm Transplantation  
Stereoisomerism  
Structure-Activity Relationship  
Thalidomide: AD, administration & dosage  
Thalidomide: AA, analogs & derivatives  
Thalidomide: CH, chemistry  
\*Thalidomide: TU, therapeutic use  
Treatment Outcome  
\*Tumor Necrosis Factor: BI, biosynthesis  
Xanthenes: AD, administration & dosage  
\*Xanthenes: TU, therapeutic use  
CAS REGISTRY NO.: 117570-53-3 (5,6-dimethylxanthenoneacetic acid); 50-35-1 (Thalidomide)  
CHEMICAL NAME: 0 (3'-methylthalidomide); 0 (3-fluorothalidomide); 0 (Angiogenesis Inhibitors); 0 (Tumor Necrosis Factor); 0 (Xanthenes)

L125 ANSWER 3 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2003501250 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 14578685  
TITLE: Phase II trial and pharmacokinetic study of thalidomide in patients with metastatic colorectal cancer.  
AUTHOR: Dal Lago Lissandra; Richter Marc F; Cancela Anna I; Fernandes Sabrina A; Jung Keylla T; Rodrigues Ana C; Costa Teresa Dalla; Di Leone Luciane P; Schwartzmann Gilberto  
CORPORATE SOURCE: Department of Medical Oncology, Faculty of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil.  
SOURCE: Investigational new drugs, (2003 Aug) 21 (3) 359-66.  
Journal code: 8309330. ISSN: 0167-6997.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE II)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200407  
ENTRY DATE: Entered STN: 20031028  
Last Updated on STN: 20040717  
Entered Medline: 20040716

## ABSTRACT:

INTRODUCTION: This study was designed to estimate the percentage of objective tumor responses; toxicity profile, and obtain additional information about the plasma pharmacokinetics of thalidomide in patients with refractory and progressing metastatic colorectal cancer. STUDY DESIGN: This phase II clinical

trial was conducted according to the two-stage Simon method with the inclusion of consecutive patients. The study protocol was approved by the Institutional Review Board (IRB) of the Academic Hospital (HCPA) of the Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil. **PATIENTS AND METHODS:** Seventeen patients with previously treated, refractory progressive metastatic colorectal cancer were eligible. Six patients had prior radiotherapy. The patients had a median of one previous chemotherapy regimen. Patients were initially treated with 200 mg/day of thalidomide with an increase in dose by 200 mg/day every 2 weeks until a final daily dose of 800 mg/day was achieved. Patients were evaluated every 8 weeks for response by radiographic criteria. Plasma pharmacokinetics studies were performed in four patients at 200 mg level and in one patient at 600 mg during the first 24 h. **MAIN OUTCOME MEASURES AND RESULTS:** A total of 17 patients were accrued, all of them being evaluable for toxicity and 14 for response. Thalidomide was well tolerated, with constipation, somnolence, dizziness, and dry mouth being the major toxicities. There were no objective response or stable disease. The median survival was 3.6 months. Single-agent thalidomide is a generally well-tolerated drug that showed no antitumor activity in patients with advanced pretreated metastatic colorectal cancer. Although thalidomide did not show antitumor activity in this patient population, future studies of this agent in patients at initial stages of the disease (when its antiangiogenic properties may be more relevant to disease progression) could be considered.

**CONTROLLED TERM:** Check Tags: Female; Human; Male  
Adult  
Aged  
Aged, 80 and over  
Angiogenesis Inhibitors: AE, adverse effects  
\*Angiogenesis Inhibitors: PK, pharmacokinetics  
Angiogenesis Inhibitors: TU; therapeutic use  
\*Colorectal Neoplasms: DT, drug therapy  
\*Colorectal Neoplasms: PA, pathology  
Disease Progression  
Dose-Response Relationship, Drug  
Middle Aged  
Thalidomide: AE, adverse effects  
\*Thalidomide: PK, pharmacokinetics  
Thalidomide: TU, therapeutic use  
Time Factors  
Treatment Outcome  
**CAS REGISTRY NO.:** 50-35-1 (Thalidomide)  
**CHEMICAL NAME:** 0 (Angiogenesis Inhibitors)

L125 ANSWER 4 OF 19 MEDLINE on STN  
**ACCESSION NUMBER:** 2003430185 MEDLINE  
**DOCUMENT NUMBER:** PubMed ID: 12943822  
**TITLE:** Anti-angiogenic effect of silymarin on colon cancer LoVo cell line.  
**AUTHOR:** Yang Shung-Haur; Lin Jen-Kou; Chen Wei-Shone; Chiu Jen-Hwey  
**CORPORATE SOURCE:** Institute of Clinical, National Yang-Ming University, Taipei, Taiwan, Republic of China.  
**SOURCE:** Journal of surgical research, (2003 Jul) 113 (1) 133-8.  
Journal code: 0376340. ISSN: 0022-4804.  
**PUB. COUNTRY:** United States  
**DOCUMENT TYPE:** Journal; Article; (JOURNAL ARTICLE)  
**LANGUAGE:** English  
**FILE SEGMENT:** Priority Journals  
**ENTRY MONTH:** 200310  
**ENTRY DATE:** Entered STN: 20030916  
Last Updated on STN: 20031022  
Entered Medline: 20031021

**ABSTRACT:**

**OBJECTIVE:** This study was designed to evaluate the anti-angiogenic effect of

silymarin (SM) and its major pure component silibinin (SB), and also thalidomide (TH). MATERIALS AND METHODS: A modified in vitro system using a coculture of endothelial (EA.hy 926) and colon cancer (LoVo) cell lines was adopted in this study. RESULTS: In cytotoxicity assay, SM/SB/TH concentrations causing 20% (IC(20)) inhibition of cellular growth were 41.8 microg/ml/0.22 mM/0.088 mM for EA.hy 926 cells, and 16.1 microg/ml/0.12 mM/0.099 mM for LoVo cells, respectively. All 3 drugs showed concentration dependent inhibition of migration and differentiation assay. The IC(50) inhibiting chemotaxis migration of EA.hy 926 towards LoVo by SM/SB/TH was 1.15 microg/ml/0.66 microM/1.98 microM, respectively. In differentiation assay, SM/SB/TH inhibited in vitro capillary tube formation by 50% at 1.25 microg/ml/2.6 micro/6.3 microM, respectively. In an analysis of vascular endothelial growth factor secreted by LoVo cells, SM/SB/TH decreased 50% secretion at 6.52 microg/ml/6.6 microM/131.7 microM, respectively. CONCLUSION: SM/SB has a strong anti-angiogenesis effect on the colon cancer cell line, and this might provide an alternative treatment option for anti-cancer treatment.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't  
\*Angiogenesis Inhibitors: PD, pharmacology  
Cell Differentiation: DE, drug effects  
Cell Movement: DE, drug effects  
\*Colonic Neoplasms: DT, drug therapy  
Colonic Neoplasms: PP, physiopathology  
Endothelial Growth Factors: AN, analysis  
\*Endothelium, Vascular: DE, drug effects  
Endothelium, Vascular: PP, physiopathology  
Intercellular Signaling Peptides and Proteins: AN, analysis  
Lymphokines: AN, analysis  
\*Silymarin: PD, pharmacology  
Thalidomide: PD, pharmacology  
Tumor Cells, Cultured: DE, drug effects  
Vascular Endothelial Growth Factor A  
Vascular Endothelial Growth Factors  
CAS REGISTRY NO.: 22888-70-6 (silybin); 50-35-1 (Thalidomide)  
CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Endothelial Growth Factors); 0 (Intercellular Signaling Peptides and Proteins); 0 (Lymphokines); 0 (Silymarin); 0 (Vascular Endothelial Growth Factor A); 0 (Vascular Endothelial Growth Factors)

L125 ANSWER 5 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2003362270 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12894521  
TITLE: Combination therapy with paclitaxel and thalidomide inhibits angiogenesis and growth of human colon cancer xenograft in mice.  
AUTHOR: Fujii Toshiyuki; Tachibana Mitsuo; Dhar Dipok Kumar; Ueda Shuhei; Kinugasa Shoichi; Yoshimura Hiroshi; Kohno Hitoshi; Nagasue Naofumi  
CORPORATE SOURCE: Second Department of Surgery, Shimane Medical University, Enya-cho 89-1, Izumo 693-8501, Shimane, Japan..  
fujii104@shimane-med.ac.jp  
SOURCE: Anticancer research, (2003 May-Jun) 23 (3B) 2405-11.  
Journal code: 8102988. ISSN: 0250-7005.  
PUB. COUNTRY: Greece  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200308  
ENTRY DATE: Entered STN: 20030805  
Last Updated on STN: 20030829  
Entered Medline: 20030828



## ABSTRACT:

BACKGROUND: Combination chemotherapy is increasingly practiced for treating malignancies with greater sensitivity and less toxicity. Paclitaxel is a potent anti-tumor agent but has dose-limiting side-effects, whereas thalidomide is an orally active anti-angiogenic drug but less than sufficient to exert anti-tumor effect as a single agent. MATERIALS AND METHODS: Nude mice bearing hypervascular (LS174T) and less vascular (HT29) colon carcinomas were challenged with either a non-cytotoxic dose of paclitaxel, thalidomide or a combination of paclitaxel and thalidomide. RESULTS: Significant growth retardation was noticed only in the combination treatment group of LS174T tumors. Microvessel density data indicated a significantly low count in the combination treatment group compared to the others. Trends of decreased expression of angiogenic growth factors and increased apoptotic index were noticed in the combination treatment group. CONCLUSION: The results of this study underscore the therapeutic efficacy of concomitant use of paclitaxel and thalidomide in the treatment of highly vascular colorectal tumors in a xenograft model.

CONTROLLED TERM: Check Tags: Human; Male  
Adenocarcinoma: BS, blood supply  
\*Adenocarcinoma: DT, drug therapy  
Adenocarcinoma: ME, metabolism  
Adenocarcinoma: PA, pathology  
Animals  
\*Antineoplastic Combined Chemotherapy Protocols: PD, pharmacology  
Apoptosis: DE, drug effects  
Cell Division: DE, drug effects  
Colonic Neoplasms: BS, blood supply  
\*Colonic Neoplasms: DT, drug therapy  
Colonic Neoplasms: ME, metabolism  
Colonic Neoplasms: PA, pathology  
Endothelial Growth Factors: BI, biosynthesis  
Endothelium, Vascular: DE, drug effects  
Fibroblast Growth Factor 2: BI, biosynthesis  
Intercellular Signaling Peptides and Proteins: BI, biosynthesis  
Lymphokines: BI, biosynthesis  
Mice  
Mice, Inbred BALB C  
Mice, Nude  
\*Neovascularization, Pathologic: DT, drug therapy  
Neovascularization, Pathologic: ME, metabolism  
Neovascularization, Pathologic: PA, pathology  
Paclitaxel: AD, administration & dosage  
Thalidomide: AD, administration & dosage  
Vascular Endothelial Growth Factor A  
Vascular Endothelial Growth Factors  
Xenograft Model Antitumor Assays  
CAS REGISTRY NO.: 103107-01-3 (Fibroblast Growth Factor 2); 33069-62-4 (Paclitaxel); 50-35-1 (Thalidomide)  
CHEMICAL NAME: 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Endothelial Growth Factors); 0 (Intercellular Signaling Peptides and Proteins); 0 (Lymphokines); 0 (Vascular Endothelial Growth Factor A); 0 (Vascular Endothelial Growth Factors)

L125 ANSWER 6 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2003147113 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12663627  
TITLE: Thalidomide-associated hyperglycemia and diabetes: case report and review of literature.  
AUTHOR: Pathak Ram D; Jayaraj Kandaswamy; Blonde Lawrence

SOURCE: Diabetes care, (2003 Apr) 26 (4) 1322-3.  
Journal code: 7805975. ISSN: 0149-5992.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)  
Letter

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200310

ENTRY DATE: Entered STN: 20030331  
Last Updated on STN: 20031030  
Entered Medline: 20031029

CONTROLLED TERM: Check Tags: Human; Male  
Aged  
\*Angiogenesis Inhibitors: AE, adverse effects  
Antineoplastic Agents: AE, adverse effects  
Blood Glucose: ME, metabolism  
\*Colonic Neoplasms: DT, drug therapy  
\*Diabetes Mellitus: CI, chemically induced  
Diabetes Mellitus: DT, drug therapy  
\*Hyperglycemia: CI, chemically induced  
\*Insulin: TU, therapeutic use  
Kidney Failure: CO, complications  
\*Multiple Myeloma: DT, drug therapy  
\*Thalidomide: AE, adverse effects  
Treatment Outcome

CAS REGISTRY NO.: 11061-68-0 (Insulin); 50-35-1 (Thalidomide)

CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents); 0 (Blood Glucose)

L125 ANSWER 7 OF 19 MEDLINE on STN

ACCESSION NUMBER: 2003055759 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12566301

TITLE: A novel subclass of thalidomide analogue with anti-solid tumor activity in which caspase-dependent apoptosis is associated with altered expression of bcl-2 family proteins.

AUTHOR: Marriott J Blake; Clarke Ian A; Czajka Anna; Dredge Keith; Childs Kay; Man Hon-Wah; Schafer Peter; Govinda Sowmya; Muller George W; Stirling David I; Dalglish Angus G

CORPORATE SOURCE: Division of Oncology, St. George's Hospital Medical School, Tooting, London SW17 0RE, United Kingdom..  
jmarriot@sgghms.ac.uk

SOURCE: Cancer research, (2003 Feb 1) 63 (3) 593-9.  
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200303

ENTRY DATE: Entered STN: 20030205  
Last Updated on STN: 20030308  
Entered Medline: 20030307

ABSTRACT: Thalidomide is clinically useful in a number of cancers. Antitumor activity may be related to a number of known properties, including anti-tumor necrosis factor (TNF)-alpha and T-cell costimulatory and antiangiogenic activities. However, it may also involve direct antitumor effects. A series of second generation thalidomide analogues have been separated into two distinct groups of compounds, each with enhanced therapeutic potential, i.e., SelCIDs, which are phosphodiesterase (PDE) type IV inhibitors, and IMiDs, which have unknown mechanism(s) of action. We report here our efforts to determine direct antitumor effects of thalidomide and compounds from both groups. We found that

one of the SelCID analogues (SelCID-3) was consistently effective at reducing tumor cell viability in a variety of solid tumor lines but had no effect on non-neoplastic cells. The antitumor activity was independent of known PDE4 inhibitory activity and did not involve cAMP elevation. Growth arrest was preceded by the early induction of G(2)-M cell cycle arrest, which led to caspase 3 mediated apoptosis. This was associated with increased expression of pro-apoptotic proteins and decreased expression of antiapoptotic bcl-2. Furthermore, extensive apoptosis in vivo was detected during SelCID-3-mediated inhibition of tumor growth in a murine xenotransplantation cancer model. Our results suggest that SelCID-3 represents a novel antitumor agent distinct from thalidomide and from previously characterized analogues with therapeutic potential against a range of solid tumors. This effect appears to be mediated via alterations in the expression of bcl-2 family proteins.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't  
Animals  
\*Antineoplastic Agents: PD, pharmacology  
\*Apoptosis: DE, drug effects  
Apoptosis: PH, physiology  
Caspases: AI, antagonists & inhibitors  
Caspases: ME, metabolism  
\*Caspases: PH, physiology  
Cell Cycle: DE, drug effects  
Cell Division: DE, drug effects  
Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: ME, metabolism  
Colorectal Neoplasms: PA, pathology  
Cyclic AMP: BI, biosynthesis  
Melanoma: DT, drug therapy  
Melanoma: ME, metabolism  
Melanoma: PA, pathology  
Membrane Proteins: BI, biosynthesis  
Mice  
Mice, Nude  
Pancreatic Neoplasms: DT, drug therapy  
Pancreatic Neoplasms: ME, metabolism  
Pancreatic Neoplasms: PA, pathology  
Prostatic Neoplasms: DT, drug therapy  
Prostatic Neoplasms: ME, metabolism  
Prostatic Neoplasms: PA, pathology  
Proto-Oncogene Proteins: BI, biosynthesis  
Proto-Oncogene Proteins c-bcl-2: AI, antagonists & inhibitors  
\*Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis  
Proto-Oncogene Proteins c-bcl-2: PH, physiology  
\*Thalidomide: AA, analogs & derivatives  
\*Thalidomide: PD, pharmacology  
Tumor Cells, Cultured  
Xenograft Model Antitumor Assays  
CAS REGISTRY NO.: 50-35-1 (Thalidomide); 60-92-4 (Cyclic AMP)  
CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Bax protein); 0 (Membrane Proteins); 0 (Proto-Oncogene Proteins); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (SelCID-3); 0 (bak protein); EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase-3)  
L125 ANSWER 8 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2002729277 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12485902  
TITLE: Thalidomide suppresses the interleukin 1beta-induced NFkappaB signaling pathway in colon cancer cells.  
AUTHOR: Jin Soo Hyun; Kim Tae Il; Han Dong Soo; Shin Sung Kwan; Kim Won Ho  
CORPORATE SOURCE: Department of Internal Medicine and Institute of

Gastroenterology, Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea.

SOURCE: Annals of the New York Academy of Sciences, (2002 Nov) 973 414-8.

Journal code: 7506858. ISSN: 0077-8923.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200302

ENTRY DATE: Entered STN: 20021221

Last Updated on STN: 20030214

Entered Medline: 20030213

ABSTRACT:

Thalidomide has been shown to have both antiinflammatory and antiangiogenic effects in several diseases. However, its cellular target and mechanism of action are poorly understood. We investigated the action mechanism of thalidomide through the NFkappaB pathway. Thalidomide inhibited interleukin (IL) 1beta-induced NFkappaB transcriptional activation and IL-8 production in Caco-2 colon cancer cells. In addition, thalidomide suppressed NFkappaB nuclear translocation, IkappaB degradation, and NFkappaB-inducing kinase (NIK)-induced NFkappaB transcriptional activation. These results suggest that the molecular target of the effects of thalidomide may be IkappaB phosphorylation by IkappaB kinase (IKK), whose activation follows NIK activation and precedes IkappaB degradation in the NFkappaB pathway.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't

**Colonic Neoplasms**

Interleukin-1: AI, antagonists & inhibitors

\*Interleukin-1: PD, pharmacology

Interleukin-8: BI, biosynthesis

NF-kappa B: DE, drug effects

\*NF-kappa B: ME, metabolism

\*Signal Transduction: DE, drug effects

\*Thalidomide: PD, pharmacology

Tumor Cells, Cultured

CAS REGISTRY NO.: 50-35-1 (Thalidomide)

CHEMICAL NAME: 0 (Interleukin-1); 0 (Interleukin-8); 0 (NF-kappa B)

L125 ANSWER 9 OF 19 MEDLINE on STN

ACCESSION NUMBER: 2002649800 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12409654

TITLE: Thalidomide and immunomodulatory drugs as cancer therapy.

AUTHOR: Raje Noopur; Anderson Kenneth C

CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Department of Adult Oncology, Dana Farber Cancer Institute, Boston, Massachusetts 02115, USA.

SOURCE: Current opinion in oncology, (2002 Nov) 14 (6) 635-40.

Ref: 53

Journal code: 9007265. ISSN: 1040-8746.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200305

ENTRY DATE: Entered STN: 20021105

Last Updated on STN: 20030503

Entered Medline: 20030502

ABSTRACT:

The demonstration of increased angiogenesis in cancer pathogenesis prompted the

use of thalidomide in both solid tumors and hematologic malignancies. Its broad spectrum of actions besides its antiangiogenic potential, specifically, its immunomodulatory properties, antiinflammatory actions, and direct effect on tumor cells and their microenvironment, provides an alternative strategy in the armamentarium against cancer. Thalidomide is being evaluated for treatment of hematologic cancers like multiple myeloma and myelodysplasia, and solid tumors like lung, breast, renal, and colon cancer. Thalidomide analogues, the immunomodulatory drugs have increased potency and have demonstrated efficacy and reduced toxicity in phase I and II clinical studies. This article reviews both laboratory-based and clinical studies with thalidomide and the immunomodulatory drugs and their application in different cancers.

CONTROLLED TERM: Check Tags: Human  
\*Adjuvants, Immunologic: PD, pharmacology  
Breast Neoplasms: DT, drug therapy  
Clinical Trials  
Colonic Neoplasms: DT, drug therapy  
\*Immunosuppressive Agents: PD, pharmacology  
Inflammation  
Kidney Neoplasms: DT, drug therapy  
Lung Neoplasms: DT, drug therapy  
Multiple Myeloma: DT, drug therapy  
Myelodysplastic Syndromes: DT, drug therapy  
Thalidomide: AA, analogs & derivatives  
\*Thalidomide: PD, pharmacology  
CAS REGISTRY NO.: 50-35-1 (Thalidomide)  
CHEMICAL NAME: 0 (Adjuvants, Immunologic); 0 (Immunosuppressive Agents)

L125 ANSWER 10 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2002410609 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12163635  
TITLE: Cooperative effect of radioimmunotherapy and antiangiogenic therapy with thalidomide in human cancer xenografts.  
AUTHOR: Kinuya Seigo; Kawashima Atsuhiko; Yokoyama Kunihiro; Koshida Kiyoshi; Konishi Shota; Watanabe Naoto; Shuke Noriyuki; Bunko Hisashi; Michigishi Takatoshi; Tonami Norihisa  
CORPORATE SOURCE: Department of Biotracer Medicine, Kanazawa University Graduate School of Medical Sciences, Japan.. kinuya@med.kanazawa-u.ac.jp  
SOURCE: Journal of nuclear medicine : official publication, Society of Nuclear Medicine, (2002 Aug) 43 (8) 1084-9. Journal code: 0217410. ISSN: 0161-5505.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200208  
ENTRY DATE: Entered STN: 20020808  
Last Updated on STN: 20020824  
Entered Medline: 20020823

ABSTRACT: Antiangiogenic therapy may prolong the dormancy of cancer lesions. Moreover, radioimmunotherapy (RIT) may eradicate this population of cells. This study dealt with determining the benefits associated with the combined usefulness of these 2 therapies with respect to inhibition of tumor growth. METHODS: Antiangiogenic therapy using oral thalidomide (daily dose, 200 mg/kg) and RIT involving a single intravenous injection (4.63 MBq (131)I-A7, an IgG1 murine monoclonal antibody) were conducted in mice bearing LS180 human colon cancer xenografts. RIT with an irrelevant IgG1, HPMS-1, was also performed as a control. Antiangiogenesis of thalidomide was investigated by immunohistochemical analysis of tumor sections. RESULTS: Antiangiogenic therapy and RIT with (131)I-A7 significantly suppressed the growth of

xenografts. This combination produced more efficient tumor growth inhibition than did the monotherapy ( $P < 0.005$ ). RIT using (131)I-HPMS-1 was far less effective than (131)I-A7, even when combined with thalidomide administration. Immunohistochemistry revealed a decrease in the microvessel number within tumors treated with thalidomide ( $P < 0.0001$ ). Combined therapy further reduced the microvessel number ( $P < 0.01$  vs. thalidomide monotherapy). CONCLUSION: The combination of RIT and thalidomide antiangiogenic therapy produces a better response of tumors than does monotherapy. Acting in concert, antiangiogenic therapy may prolong the dormancy of cancer lesions and RIT may eradicate this population of cells.

CONTROLLED TERM: Check Tags: Female; Human; Support, Non-U.S. Gov't  
\*Angiogenesis Inhibitors: TU, therapeutic use  
Animals  
Antibodies, Monoclonal: TU, therapeutic use  
\*Colonic Neoplasms: TH, therapy  
Iodine Radioisotopes  
Mice  
Mice, Inbred BALB C  
Mice, Nude  
Neoplasm Transplantation  
\*Radioimmunotherapy  
\*Thalidomide: TU, therapeutic use  
Time Factors  
Transplantation, Heterologous  
CAS REGISTRY NO.: 50-35-1 (Thalidomide)  
CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antibodies, Monoclonal); 0 (Iodine Radioisotopes)

L125 ANSWER 11 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2002298600 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12040298  
TITLE: Thalidomide and irinotecan-associated diarrhea.  
AUTHOR: Tchekmedyian N Simon  
SOURCE: American journal of clinical oncology : official publication of the American Radium Society, (2002 Jun) 25 (3) 324.  
Journal code: 8207754. ISSN: 0277-3732.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CASE REPORTS)  
Letter  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200206  
ENTRY DATE: Entered STN: 20020602  
Last Updated on STN: 20020628  
Entered Medline: 20020627  
CONTROLLED TERM: Check Tags: Female; Human  
Adenocarcinoma: DT, drug therapy  
Adenocarcinoma: SC, secondary  
Aged  
Aged, 80 and over  
\*Antineoplastic Agents, Phytogenic: AE, adverse effects  
\*Camptothecin: AE, adverse effects  
Camptothecin: AA, analogs & derivatives  
\*Diarrhea: CI, chemically induced  
Diarrhea: PC, prevention & control  
\*Immunosuppressive Agents: TU, therapeutic use  
Lung Neoplasms: DT, drug therapy  
Lung Neoplasms: SC, secondary  
Rectal Neoplasms: DT, drug therapy  
Rectal Neoplasms: PA, pathology  
\*Thalidomide: TU, therapeutic use

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 50-35-1 (Thalidomide); 7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic); 0 (Immunosuppressive Agents)

L125 ANSWER 12 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2002274258 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12014864  
TITLE: Irinotecan/thalidomide in metastatic colorectal cancer.  
AUTHOR: Govindarajan Rangaswamy  
CORPORATE SOURCE: University of Arkansas for Medical Sciences, Little Rock 72205, USA.. govindarajanrang@uams.edu  
SOURCE: Oncology (Williston Park, N.Y.), (2002 Apr) 16 (4 Suppl 3) 23-6. Ref: 17  
Journal code: 8712059. ISSN: 0890-9091.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200211  
ENTRY DATE: Entered STN: 20020517  
Last Updated on STN: 20021211  
Entered Medline: 20021107

## ABSTRACT:

The prognosis for patients with metastatic colorectal cancer is poor. Use of irinotecan (CPT-11, Camptosar) results in modest response rates of approximately 20% in refractory patients diagnosed with this advanced stage of disease and offers a side-effect profile that improves on that of previous standard treatments. Thalidomide (Thalomid) has antiangiogenic properties, and angiogenesis has been shown to influence the outcome of colon cancer patients. A good response rate and acceptable tolerability regarding gastrointestinal effects were demonstrated in a pilot study of the irinotecan/thalidomide combination in patients with metastatic colorectal cancer. This combination is being assessed at the University of Arkansas for Medical Sciences as second-line therapy in a phase II trial. Patients with metastatic colorectal cancer are receiving 350 mg/m<sup>2</sup> of irinotecan every 3 weeks plus 400 mg/m<sup>2</sup>/d of thalidomide. Preliminary response and safety data are presented for 18 enrolled patients.

CONTROLLED TERM: Check Tags: Human  
Adult  
Aged  
\*Angiogenesis Inhibitors: TU, therapeutic use  
\*Antineoplastic Agents, Phytogenic: TU, therapeutic use  
\*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use  
\*Camptothecin: AA, analogs & derivatives  
\*Camptothecin: TU, therapeutic use  
Clinical Trials  
\*Colorectal Neoplasms: DT, drug therapy  
Middle Aged  
Neoplasm Metastasis  
\*Thalidomide: TU, therapeutic use

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 50-35-1 (Thalidomide); 7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Phytogenic); 0 (Antineoplastic Combined Chemotherapy Protocols)

L125 ANSWER 13 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2001192568 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11204671  
TITLE: Irinotecan and thalidomide in metastatic colorectal cancer.  
AUTHOR: Govindarajan R  
CORPORATE SOURCE: Division of Hematology/Oncology, University of Arkansas for  
Medical Sciences, Little Rock, Arkansas, USA.  
SOURCE: Oncology (Williston Park, N.Y.), (2000 Dec) 14 (12 Suppl  
13) 29-32.  
Journal code: 8712059. ISSN: 0890-9091.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CASE REPORTS)  
(CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE II)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200104  
ENTRY DATE: Entered STN: 20010410  
Last Updated on STN: 20010410  
Entered Medline: 20010405

## ABSTRACT:

Fifteen patients with metastatic colorectal cancer were treated with irinotecan (CPT-11, Camptosar) at 300 to 350 mg/m<sup>2</sup> every 21 days and thalidomide (Thalomid) at 400 mg/d. Of the 15 patients, 11 were in a pilot study and 4 were in an ongoing phase II protocol. There were 12 men and 3 women, with a median age of 56 years (range: 29 to 79 years). Patients were treated with a median of three cycles (range: one to eight cycles). The four patients enrolled in the formal protocol were not evaluable for response at the time of this report. Of the 11 patients in the pilot study, 10 were evaluable for response; there were two complete responses, two partial responses, and six progressions. Investigators noted a remarkable absence of grade 3/4 gastrointestinal toxicities, and concluded that further testing of the complete response and toxicity profile of the irinotecan/thalidomide regimen was warranted.

CONTROLLED TERM: Check Tags: Female; Human; Male  
Adult  
Aged  
\*Angiogenesis Inhibitors: TU, therapeutic use  
\*Antineoplastic Agents, Phytogenic: TU, therapeutic use  
\*Antineoplastic Combined Chemotherapy Protocols: TU,  
therapeutic use  
\*Camptothecin: AA, analogs & derivatives  
\*Camptothecin: TU, therapeutic use  
Camptothecin: TO, toxicity  
\*Colorectal Neoplasms: DT, drug therapy  
Middle Aged  
Neoplasm Metastasis  
Pilot Projects  
\*Thalidomide: TU, therapeutic use  
Thalidomide: TO, toxicity  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 50-35-1 (Thalidomide); 7689-03-4  
(Camptothecin)  
CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents,  
Phytogenic); 0 (Antineoplastic Combined Chemotherapy  
Protocols)

L125 ANSWER 14 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2000456453 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10972483  
TITLE: Modulation of the pharmacokinetics of the antitumour agent  
5,6-dimethylxanthenone-4-acetic acid (DMXAA) in mice by  
thalidomide.  
AUTHOR: Kestell P; Zhao L; Baguley B C; Palmer B D; Muller G;



CORPORATE SOURCE: Paxton J W; Ching L M  
Auckland Cancer Society Research Centre, University of  
Auckland Medical School, New Zealand.  
SOURCE: Cancer chemotherapy and pharmacology, (2000) 46 (2) 135-41.  
Journal code: 7806519. ISSN: 0344-5704.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; AIDS  
ENTRY MONTH: 200009  
ENTRY DATE: Entered STN: 20001005  
Last Updated on STN: 20001005  
Entered Medline: 20000925

## ABSTRACT:

BACKGROUND: 5,6-Dimethylxanthenone-4-acetic acid (DMXAA), an investigative drug currently in clinical trial, acts on tumour vasculature through the induction of cytokines. Coadministration of thalidomide, a modulator of cytokine production, potentiates the antitumour activity of DMXAA against the murine Colon 38 carcinoma in mice. We wished to determine whether alteration of the pharmacokinetics of DMXAA by thalidomide could provide an explanation for this potentiation. RESULTS: Coadministration of thalidomide to Colon 38 tumour-bearing mice significantly ( $P < 0.05$ ) increased the elimination half-life ( $t_{1/2}$ ) of DMXAA in plasma (413 micromol/l), liver (132 micromol/l), and spleen (77 micromol/l), and significantly ( $P < 0.05$ ) increased DMXAA concentrations in Colon 38 tumour tissue (0.25-4.5 h). L-Thalidomide had a greater effect on DMXAA elimination ( $P < 0.01$ ) than did D-thalidomide or the racemate. Coadministration of thalidomide increased the area under the concentration-time curve (AUC) of DMXAA by 1.8-fold in plasma, liver and spleen, and by 3.0-fold in tumour. Bile from mice given thalidomide and DMXAA contained substantially lower amounts of the glucuronide metabolite of DMXAA (DMXAA-G) than did bile from mice given DMXAA alone. CONCLUSION: Glucuronidation is a major excretory pathway for DMXAA in the mouse. Thalidomide, probably as the L-form, decreases the rate of elimination of DMXAA from plasma, spleen, liver and tumour by altering the rate of glucuronidation. The reduction in the elimination of DMXAA by thalidomide may lead to a selective increase in exposure of tumour tissue to drug, providing a basis for its potentiation of antitumour activity.

CONTROLLED TERM: Check Tags: Female; Support, Non-U.S. Gov't  
Animals  
Antineoplastic Agents: BL, blood  
\*Antineoplastic Agents: PK, pharmacokinetics  
Area Under Curve  
Bile: ME, metabolism  
Colonic Neoplasms: BL, blood  
\*Colonic Neoplasms: ME, metabolism  
Half-Life  
Mice  
Mice, Inbred C57BL  
Stereoisomerism  
\*Thalidomide: PD, pharmacology  
Time Factors  
Tissue Distribution: DE, drug effects  
Xanthenes: BL, blood  
\*Xanthenes: PK, pharmacokinetics  
\*Xanthenes

CAS REGISTRY NO.: 117570-53-3 (5,6-dimethylxanthenoneacetic acid); 50-35-1  
(Thalidomide)  
CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Xanthenes); 0 (Xanthenes)

L125 ANSWER 15 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 2000182194 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10717731

TITLE: Thalidomide for night sweats in patients with advanced cancer.

COMMENT: Comment on: Palliat Med. 1998 May;12(3):208-9. PubMed ID: 9743843

AUTHOR: Calder K; Bruera E

SOURCE: Palliative medicine, (2000 Jan) 14 (1) 77-8.  
Journal code: 8704926. ISSN: 0269-2163.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: (CASE REPORTS)  
Commentary  
Letter

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 200004

ENTRY DATE: Entered STN: 20000413  
Last Updated on STN: 20000525  
Entered Medline: 20000407

CONTROLLED TERM: Check Tags: Female; Human  
Adenocarcinoma: DT, drug therapy  
Adenocarcinoma: PP, physiopathology  
Cachexia: DT, drug therapy  
**Colonic Neoplasms: DT, drug therapy**  
**Colonic Neoplasms: PP, physiopathology**  
\*Hypnotics and Sedatives: TU, therapeutic use  
Middle Aged  
\*Sweating: DE, drug effects  
**\*Thalidomide: TU, therapeutic use**

CAS REGISTRY NO.: 50-35-1 (Thalidomide)

CHEMICAL NAME: 0 (Hypnotics and Sedatives)

L125 ANSWER 16 OF 19 MEDLINE on STN

ACCESSION NUMBER: 1999108650 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9891501

TITLE: Suppression of serum tumour necrosis factor-alpha by thalidomide does not lead to reversal of tumour vascular collapse and anti-tumour activity of 5,6-dimethylxanthenone-4-acetic acid.

AUTHOR: Browne W L; Wilson W R; Baguley B C; Ching L M

CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland School of Medicine, New Zealand.

SOURCE: Anticancer research, (1998 Nov-Dec) 18 (6A) 4409-13.  
Journal code: 8102988. ISSN: 0250-7005.

PUB. COUNTRY: Greece

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199902

ENTRY DATE: Entered STN: 19990223  
Last Updated on STN: 19990223  
Entered Medline: 19990211

ABSTRACT:  
The antitumour agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA), developed in this laboratory as a potent analogue of flavone acetic acid (FAA), has a novel antitumour action involving both immune and vascular components. DMXAA induces the synthesis of tumour necrosis factor-alpha (TNF) and it has been hypothesised that this mediates its selective reduction of tumour blood flow and consequent induction of tumour necrosis. Unexpectedly, the drug thalidomide, while reducing the serum TNF response to DMXAA, potentiates its antitumour effect. We have investigated this in the MDAH-MCa-4 mammary carcinoma model, comparing it to previous data with the Colon 38 adenocarcinoma. We have related DMXAA-induced blood flow changes in the MCa-4 tumour to tumour growth delay, serum TNF and extractable TNF from tumour

tissue. We have also compared the effect of thalidomide (387  $\mu\text{mol/kg}$ ) on DMXAA (80  $\mu\text{mol/kg}$ ) with that of a monoclonal anti-TNF antibody (50 micrograms/mouse). We find that tumour blood flow reduction is strongly correlated with tumour growth delay. Coadministration of anti-TNF antibody abolishes serum TNF levels and slightly reduces the antitumour effects of DMXAA. While tumour growth delay is not correlated with serum induced TNF levels, it is related to tumour TNF levels. We conclude that while the data are consistent with TNF being the principal mediator of the action of DMXAA, serum TNF levels do not reflect the antitumour response.

CONTROLLED TERM: Check Tags: Female; Support, Non-U.S. Gov't

Adenocarcinoma

Animals

\*Antineoplastic Agents: TU, therapeutic use

Colonic Neoplasms

Mammary Neoplasms, Experimental: BL, blood

\*Mammary Neoplasms, Experimental: BS, blood supply

\*Mammary Neoplasms, Experimental: DT, drug therapy

Mammary Neoplasms, Experimental: IM, immunology

Mice

Mice, Inbred C3H

Mice, Inbred C57BL

Mice, Inbred DBA

Necrosis

Neovascularization, Pathologic: PA, pathology

Neovascularization, Pathologic: PC, prevention & control

Regional Blood Flow: DE, drug effects

\*Thalidomide: TU, therapeutic use

Tumor Necrosis Factor: AI, antagonists & inhibitors

\*Tumor Necrosis Factor: BI, biosynthesis

\*Xanthenes: TU, therapeutic use

\*Xanthenes

CAS REGISTRY NO.: 117570-53-3 (5,6-dimethylxanthenoneacetic acid); 50-35-1 (Thalidomide)

CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Tumor Necrosis Factor); 0 (Xanthenes); 0 (Xanthenes)

L125 ANSWER 17 OF 19 MEDLINE on STN

ACCESSION NUMBER: 1998366839 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9703279

TITLE: Interaction of thalidomide, phthalimide analogues of thalidomide and pentoxifylline with the anti-tumour agent 5,6-dimethylxanthenone-4-acetic acid: concomitant reduction of serum tumour necrosis factor-alpha and enhancement of anti-tumour activity.

AUTHOR: Ching L M; Browne W L; Tchernegovski R; Gregory T; Baguley B C; Palmer B D

CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland School of Medicine, New Zealand.

SOURCE: British journal of cancer, (1998 Aug) 78 (3) 336-43. Journal code: 0370635. ISSN: 0007-0920.

PUB. COUNTRY: SCOTLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199808

ENTRY DATE: Entered STN: 19980903

Last Updated on STN: 19980903

Entered Medline: 19980824

ABSTRACT:

DMXAA (5,6-dimethylxanthenone-4-acetic acid), a novel anti-tumour agent currently undergoing clinical evaluation, appears to mediate its anti-tumour effects through immune modulation and the production of the cytokine tumour

necrosis factor-alpha (TNF). Our previous studies have shown that thalidomide, a potent inhibitor of TNF biosynthesis that has numerous biological effects, including inhibition of tumour angiogenesis, unexpectedly augments the anti-tumour response in mice to DMXAA. We show here that thalidomide (100 mg kg<sup>-1</sup>) has no effect when administered with inactive doses of DMXAA, and that it must be given simultaneously with an active dose of DMXAA to have its maximum potentiating effect on the growth of the murine Colon 38 adenocarcinoma. To address the issue of whether inhibition of serum TNF production is important for potentiation of anti-tumour activity, we have tested three potent analogues of thalidomide. All three analogues, when co-administered with DMXAA to mice at doses lower than those used with thalidomide, inhibited TNF production and were effective in potentiating the anti-tumour activity of DMXAA against transplanted Colon 38 tumours. One of the analogues, N-phenethyltetrafluorophthalimide, was 1000-fold more potent than thalidomide and at a dose of 0.1 mg kg<sup>-1</sup> in combination with DMXAA (30 mg kg<sup>-1</sup>) cured 100% of mice, compared with 67% for the group treated with DMXAA alone. We also tested pentoxifylline and found it to suppress TNF production in response to DMXAA and to potentiate the anti-tumour effect of DMXAA. The results are compatible with the hypothesis that pharmacological reduction of serum TNF levels might benefit the anti-tumour effects of DMXAA and suggest new strategies for therapy using this agent.

CONTROLLED TERM: Check Tags: Support, Non-U.S. Gov't  
Animals  
Antineoplastic Agents: CH, chemistry  
Antineoplastic Agents: TU, therapeutic use  
Colonic Neoplasms: DT, drug therapy  
Drug Synergism  
Mice  
Neoplasm Transplantation  
\*Pentoxifylline: PD, pharmacology  
Phthalimides: PD, pharmacology  
Thalidomide: AA, analogs & derivatives  
\*Thalidomide: CH, chemistry  
Thalidomide: PD, pharmacology  
Thalidomide: TU, therapeutic use  
Time Factors  
\*Tumor Necrosis Factor: ME, metabolism  
\*Xanthenes: CH, chemistry  
Xanthenes: TU, therapeutic use  
\*Xanthoness  
CAS REGISTRY NO.: 117570-53-3 (5,6-dimethylxanthenoneacetic acid); 50-35-1 (Thalidomide); 6493-05-6 (Pentoxifylline); 85-41-6 (phthalimide)  
CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Phthalimides); 0 (Tumor Necrosis Factor); 0 (Xanthenes); 0 (Xanthoness)

L125 ANSWER 18 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 97194802 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9042240  
TITLE: Failure of thalidomide to inhibit tumor growth and angiogenesis in vivo.  
AUTHOR: Gutman M; Szold A; Ravid A; Lazauskas T; Merimsky O; Klausner J M  
CORPORATE SOURCE: Department of Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv University, Israel.  
SOURCE: Anticancer research, (1996 Nov-Dec) 16 (6B) 3673-7.  
Journal code: 8102988. ISSN: 0250-7005.  
PUB. COUNTRY: Greece  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; AIDS  
ENTRY MONTH: 199703

ENTRY DATE: Entered STN: 19970407  
Last Updated on STN: 19970407  
Entered Medline: 19970327

**ABSTRACT:**

Thalidomide was recently suggested to be angiogenesis-inhibitor following the demonstration of its activity in a rabbit cornea micropocket model. The purpose of the present study was to test its efficacy in solid tumors in mice. B16-F10 melanoma and CT-26 colon carcinoma cells were injected subcutaneously, intravenously and intraperitoneally, and mice received daily gavage of 0.3-1.0 mg thalidomide starting either two or 10 days following tumor cell injection. The tumors were measured and compared with controls. There was no growth retardation in CT-26 bearing mice nor in mice with pulmonary or peritoneal metastases of B16-F10 melanoma. In 3/7 groups of mice with SC B16-F10 tumors, growth retardation was demonstrated, however the difference was not statistically significant. All tumors eventually reached maximal size, similar to controls. Morphological evaluation of the blood vessels oriented towards the tumor revealed that in both thalidomide and control groups, all mice had developed an intact network of new blood vessels. In our model for the oral administration of thalidomide inhibition of tumor growth and angiogenesis did not occur. We hypothesize that the lack of sustained antiangiogenic response was either due to immune modulation or to tumor heterogeneity and adaptation.

CONTROLLED TERM: Check Tags: Female; Support, Non-U.S. Gov't  
Animals  
\*Antineoplastic Agents: TU, therapeutic use  
Cell Division: DE, drug effects  
Colonic Neoplasms: BS, blood supply  
Colonic Neoplasms: DT, drug therapy  
Colonic Neoplasms: PA, pathology  
Drug Screening Assays, Antitumor  
Melanoma, Experimental: BS, blood supply  
Melanoma, Experimental: DT, drug therapy  
Melanoma, Experimental: PA, pathology  
Mice  
Mice, Inbred BALB C  
Mice, Inbred C57BL  
Neoplasms: BS, blood supply  
\*Neoplasms: DT, drug therapy  
Neoplasms: PA, pathology  
\*Neovascularization, Pathologic: PC, prevention & control  
\*Thalidomide: TU, therapeutic use  
Tumor Cells, Cultured  
CAS REGISTRY NO.: 50-35-1 (Thalidomide)  
CHEMICAL NAME: 0 (Antineoplastic Agents)

L125 ANSWER 19 OF 19 MEDLINE on STN  
ACCESSION NUMBER: 95367484 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7640215  
TITLE: Effect of thalidomide on tumour necrosis factor production and anti-tumour activity induced by 5,6-dimethylxanthenone-4-acetic acid.  
AUTHOR: Ching L M; Xu Z F; Gummer B H; Palmer B D; Joseph W R; Baguley B C  
CORPORATE SOURCE: Cancer Research Laboratory, University of Auckland School of Medicine, New Zealand.  
SOURCE: British journal of cancer, (1995 Aug) 72 (2) 339-43.  
Journal code: 0370635. ISSN: 0007-0920.  
PUB. COUNTRY: SCOTLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199509  
ENTRY DATE: Entered STN: 19950930

Last Updated on STN: 19980206

Entered Medline: 19950921

## ABSTRACT:

The investigational anti-tumour agent, 5,6-dimethylxanthenone-4-acetic acid (5,6-MeXAA), an analogue of flavone acetic acid (FAA), has been scheduled for clinical evaluation. Like FAA, 5,6-MeXAA exhibits excellent experimental anti-tumour activity and is an efficient inducer of cytokines in mice. We have examined the effect of pharmacological suppression of tumour necrosis factor (TNF) production on the anti-tumour activity of 5,6-MeXAA, taking advantage of previous observations that TNF production in response to endotoxin in vitro is inhibited by thalidomide. Thalidomide at doses of between 8 and 250 mg kg<sup>-1</sup> efficiently suppressed serum TNF activity in response to 5,6-MeXAA at its optimal TNF inducing dose of 55 mg kg<sup>-1</sup>. Suppression was achieved when thalidomide was administered at the same time as, or up to 4 h before, 5,6-MeXAA. Under conditions in which TNF activity was suppressed, the degree of tumour haemorrhagic necrosis and the proportion of cures in the subcutaneous Colon 38 tumour were increased. In mice administered thalidomide (100 mg kg<sup>-1</sup>) together with 5,6-MeXAA (30 mg kg<sup>-1</sup>), complete tumour regression was obtained in 100% of mice, as compared with 67% in mice receiving 5,6-MeXAA alone. The results suggest a possible new application for thalidomide and pose new questions about the action of 5,6-MeXAA and related compounds.

CONTROLLED TERM: Animals

\*Antineoplastic Agents: PD, pharmacology

Colonic Neoplasms: DT, drug therapy

Colonic Neoplasms: ME, metabolism

Drug Interactions

Mice

Mice, Inbred C57BL

Mice, Inbred DBA

Neoplasm Transplantation

\*Thalidomide: PD, pharmacology

\*Tumor Necrosis Factor: BI, biosynthesis

Tumor Necrosis Factor: ME, metabolism

\*Xanthenes: PD, pharmacology

\*Xanthonenes

CAS REGISTRY NO.: 117570-53-3 (5,6-dimethylxanthenoneacetic acid); 50-35-1 (Thalidomide)

CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Tumor Necrosis Factor); 0 (Xanthenes); 0 (Xanthonenes)

=> fil medl; d que l66; fil embase; d que l98; d que l102; s l98 or l102  
FILE 'MEDLINE' ENTERED AT 13:15:17 ON 20 JUL 2004

FILE LAST UPDATED: 17 JUL 2004 (20040717/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L37	2628	SEA FILE=MEDLINE ABB=ON	THALIDOMIDE/CT
L41	55065	SEA FILE=MEDLINE ABB=ON	ANTINEOPLASTIC COMBINED CHEMOTHERAPY PROTOCOLS/CT
L59	598909	SEA FILE=MEDLINE ABB=ON	ANTINEOPLASTIC AGENTS+NT/CT
L60	71530	SEA FILE=MEDLINE ABB=ON	L59 (L) AE/CT
L63	12718	SEA FILE=MEDLINE ABB=ON	L41 (L) AE/CT
L65	1164	SEA FILE=MEDLINE ABB=ON	L37 (L) (AE OR TO OR PO)/CT
L66	7	SEA FILE=MEDLINE ABB=ON	L60 AND L37 NOT (L65 OR L63)

*AE = adverse effect  
TO = toxicity  
PO = poisoning*

FILE 'EMBASE' ENTERED AT 13:15:17 ON 20 JUL 2004  
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE COVERS 1974 TO 15 Jul 2004 (20040715/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L67	5431	SEA FILE=EMBASE ABB=ON	THALIDOMIDE/CT OR THALIDOMIDE DERIVATIV E/CT
L72	3299	SEA FILE=EMBASE ABB=ON	L67 (L) (AD OR DO OR PD OR PK OR DT)/CT
L82	549909	SEA FILE=EMBASE ABB=ON	ANTINEOPLASTIC AGENT+NT/CT
L91	65835	SEA FILE=EMBASE ABB=ON	L82 (L) AE/CT
L93	1410	SEA FILE=EMBASE ABB=ON	L72/MAJ
L94	128	SEA FILE=EMBASE ABB=ON	L93 AND L91
L95	1242	SEA FILE=EMBASE ABB=ON	L67 (L) AE/CT
L96	18	SEA FILE=EMBASE ABB=ON	L94 NOT L95
L97	8076	SEA FILE=EMBASE ABB=ON	SIDE EFFECT#/TI
L98	1	SEA FILE=EMBASE ABB=ON	L96 AND L97

*AD - administration  
DO - dosage  
PD - pharmacology  
PK - pharmacokinetics  
DT - drug therapy  
AE - adverse effect*

L67	5431	SEA FILE=EMBASE ABB=ON	THALIDOMIDE/CT OR THALIDOMIDE DERIVATIV E/CT
L72	3299	SEA FILE=EMBASE ABB=ON	L67 (L) (AD OR DO OR PD OR PK OR DT)/CT
L82	549909	SEA FILE=EMBASE ABB=ON	ANTINEOPLASTIC AGENT+NT/CT
L91	65835	SEA FILE=EMBASE ABB=ON	L82 (L) AE/CT
L93	1410	SEA FILE=EMBASE ABB=ON	L72/MAJ
L94	128	SEA FILE=EMBASE ABB=ON	L93 AND L91
L95	1242	SEA FILE=EMBASE ABB=ON	L67 (L) AE/CT

L96 18 SEA FILE=EMBASE ABB=ON L94 NOT L95  
 L99 300202 SEA FILE=EMBASE ABB=ON SIDE EFFECT/CT  
 L100 17 SEA FILE=EMBASE ABB=ON L96 AND L99  
 L101 92 SEA FILE=EMBASE ABB=ON L67(L) IT/CT  
 L102 2 SEA FILE=EMBASE ABB=ON L101 AND L100

*IT - drug interaction*

L126 2 L98 OR L102

=> dup rem 166,1126

FILE 'MEDLINE' ENTERED AT 13:15:22 ON 20 JUL 2004

FILE 'EMBASE' ENTERED AT 13:15:22 ON 20 JUL 2004

COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

PROCESSING COMPLETED FOR L66

PROCESSING COMPLETED FOR L126

L127 9 DUP REM L66 L126 (0 DUPLICATES REMOVED)  
 ANSWERS '1-7' FROM FILE MEDLINE  
 ANSWERS '8-9' FROM FILE EMBASE

=> d iall 1-9

L127 ANSWER 1 OF 9 MEDLINE on STN  
 ACCESSION NUMBER: 2004008813 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 14705499  
 TITLE: Medication sheets for patients. Oral chemotherapy.  
 AUTHOR: Anonymous  
 SOURCE: Clinical journal of oncology nursing, (2003 Nov-Dec) 7 (6  
 Suppl) 40-72.  
 Journal code: 9705336. ISSN: 1092-1095.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (PATIENT EDUCATION HANDOUT)  
 LANGUAGE: English  
 FILE SEGMENT: Nursing Journals  
 ENTRY MONTH: 200402  
 ENTRY DATE: Entered STN: 20040107  
 Last Updated on STN: 20040207  
 Entered Medline: 20040206  
 CONTROLLED TERM: Check Tags: Human  
 Administration, Oral  
 Altretamine: AD, administration & dosage  
 \*Antineoplastic Agents: AD, administration & dosage  
 Antineoplastic Agents: AE, adverse effects  
 Busulfan: AD, administration & dosage  
 Chlorambucil: AD, administration & dosage  
 Cyclophosphamide: AD, administration & dosage  
 Dacarbazine: AD, administration & dosage  
 \*Dacarbazine: AA, analogs & derivatives  
 Deoxycytidine: AD, administration & dosage  
 \*Deoxycytidine: AA, analogs & derivatives  
 Drug Interactions  
 Drug Storage  
 Etoposide: AD, administration & dosage  
 Hydroxyurea: AD, administration & dosage  
 Lomustine: AD, administration & dosage  
 Melphalan: AD, administration & dosage  
 Methotrexate: AD, administration & dosage  
 Piperazines: AD, administration & dosage  
 Procarbazine: AD, administration & dosage  
 Pyrimidines: AD, administration & dosage



Quinazolines: AD, administration & dosage  
Safety Management  
Self Administration: AE, adverse effects  
\*Self Administration: MT, methods  
Tetrahydronaphthalenes: AD, administration & dosage  
Thalidomide: AD, administration & dosage

CAS REGISTRY NO.: 127-07-1 (Hydroxyurea); 13010-47-4 (Lomustine); 148-82-3 (Melfalan); 152459-95-5 (imatinib); 154361-50-9 (capecitabine); 184475-35-2 (Gefitinib); 305-03-3 (Chlorambucil); 33419-42-0 (Etoposide); 4342-03-4 (Dacarbazine); 50-18-0 (Cyclophosphamide); 50-35-1 (Thalidomide); 55-98-1 (Busulfan); 59-05-2 (Methotrexate); 645-05-6 (Altretamine); 671-16-9 (Procarbazine); 85622-93-1 (temozolomide); 951-77-9 (Deoxycytidine)

CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Piperazines); 0 (Pyrimidines); 0 (Quinazolines); 0 (Tetrahydronaphthalenes); 0 (bexarotene)

L127 ANSWER 2 OF 9 MEDLINE on STN  
ACCESSION NUMBER: 2002298600 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12040298  
TITLE: Thalidomide and irinotecan-associated diarrhea.  
AUTHOR: Tchekmedyian N Simon  
SOURCE: American journal of clinical oncology : official publication of the American Radium Society, (2002 Jun) 25 (3) 324.

Journal code: 8207754. ISSN: 0277-3732.

PUB. COUNTRY: United States  
DOCUMENT TYPE: (CASE REPORTS)

Letter

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200206

ENTRY DATE: Entered STN: 20020602

Last Updated on STN: 20020628

Entered Medline: 20020627

CONTROLLED TERM: Check Tags: Female; Human  
Adenocarcinoma: DT, drug therapy  
Adenocarcinoma: SC, secondary  
Aged  
Aged, 80 and over

\*Antineoplastic Agents, Phytogenic: AE, adverse effects

\*Camptothecin: AE, adverse effects

Camptothecin: AA, analogs & derivatives

\*Diarrhea: CI, chemically induced

Diarrhea: PC, prevention & control

\*Immunosuppressive Agents: TU, therapeutic use

Lung Neoplasms: DT, drug therapy

Lung Neoplasms: SC, secondary

Rectal Neoplasms: DT, drug therapy

Rectal Neoplasms: PA, pathology

\*Thalidomide: TU, therapeutic use

CAS REGISTRY NO.: 100286-90-6 (irinotecan); 50-35-1 (Thalidomide); 7689-03-4 (Camptothecin)

CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic); 0 (Immunosuppressive Agents)

L127 ANSWER 3 OF 9 MEDLINE on STN  
ACCESSION NUMBER: 2000414475 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10950238  
TITLE: Effect of thalidomide on gastrointestinal toxic effects of

irinotecan.  
AUTHOR: Govindarajan R; Heaton K M; Broadwater R; Zeitlin A; Lang N  
P; Hauer-Jensen M  
SOURCE: Lancet, (2000 Aug 12) 356 (9229) 566-7.  
Journal code: 2985213R. ISSN: 0140-6736.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Letter  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS  
ENTRY MONTH: 200008  
ENTRY DATE: Entered STN: 20000907  
Last Updated on STN: 20000907  
Entered Medline: 20000829

## ABSTRACT:

Irinotecan is the only accepted second-line treatment for colorectal cancer in the USA. Doses are, however, frequently limited by associated late-onset diarrhoea. Thalidomide has antiangiogenic and immunomodulatory properties and is being investigated as an antineoplastic. We did a pilot study of combination therapy with thalidomide and irinotecan for metastatic colorectal cancer. In an interim analysis of nine patients, thalidomide had almost eliminated the dose-limiting gastrointestinal toxic effects of irinotecan, especially diarrhoea and nausea (each  $p < 0.0001$ ), and eight of nine patients were able to complete the chemotherapy course.

CONTROLLED TERM: Check Tags: Human  
Antineoplastic Agents, Phytogenic: AD, administration & dosage  
**\*Antineoplastic Agents, Phytogenic: AE, adverse effects**  
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use  
Camptothecin: AD, administration & dosage  
**Camptothecin: AE, adverse effects**  
\*Camptothecin: AA, analogs & derivatives  
Colorectal Neoplasms: DT, drug therapy  
Colorectal Neoplasms: PA, pathology  
Diarrhea: CI, chemically induced  
Diarrhea: PC, prevention & control  
\*Digestive System: DE, drug effects  
Pilot Projects  
**Thalidomide: AD, administration & dosage**  
**\*Thalidomide: TU, therapeutic use**  
CAS REGISTRY NO.: 100286-90-6 (irinotecan); 50-35-1 (Thalidomide); 7689-03-4 (Camptothecin)  
CHEMICAL NAME: 0 (Antineoplastic Agents, Phytogenic); 0 (Antineoplastic Combined Chemotherapy Protocols)

L127 ANSWER 4 OF 9 MEDLINE on STN  
ACCESSION NUMBER: 1998271244 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9608317  
TITLE: Update on immunosuppressive therapy.  
AUTHOR: Singer N G; McCune W J  
CORPORATE SOURCE: 536 RB & C, Division of Pediatric Immunology Allergy and Rheumatology, Cleveland, OH 44106, USA.  
SOURCE: Current opinion in rheumatology, (1998 May) 10 (3) 169-73.  
Ref: 16  
Journal code: 9000851. ISSN: 1040-8711.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS  
ENTRY MONTH: 199808  
ENTRY DATE: Entered STN: 19980817  
Last Updated on STN: 19980817  
Entered Medline: 19980803

## ABSTRACT:

In this review we summarize selected articles that have been published about immunosuppressive agents in the past year. These studies fall into three major categories: 1) use of pulse cyclophosphamide in autoimmune diseases other than systemic lupus erythematosus; 2) use of newer immunosuppressive agents such as cyclosporine and FK506 in a variety of rheumatic diseases; and 3) toxicity.

CONTROLLED TERM: Check Tags: Human  
Adult  
Arthritis, Juvenile Rheumatoid: DT, drug therapy  
**Azathioprine: AE, adverse effects**  
Azathioprine: TU, therapeutic use  
Behcet Syndrome: DT, drug therapy  
Child  
Cladribine: TU, therapeutic use  
Cyclophosphamide: AD, administration & dosage  
Cyclophosphamide: TU, therapeutic use  
Cyclosporine: TU, therapeutic use  
Drug Therapy, Combination  
Hydroxychloroquine: AD, administration & dosage  
Hydroxychloroquine: AE, adverse effects  
Hydroxychloroquine: TU, therapeutic use  
Immunosuppressive Agents: AD, administration & dosage  
Immunosuppressive Agents: AE, adverse effects  
\*Immunosuppressive Agents: TU, therapeutic use  
Liver: DE, drug effects  
Liver: IN, injuries  
Lung: DE, drug effects  
Lung: IN, injuries  
Lupus Erythematosus, Systemic: DT, drug therapy  
Methotrexate: AD, administration & dosage  
**Methotrexate: AE, adverse effects**  
Methotrexate: TU, therapeutic use  
Pemphigoid, Benign Mucous Membrane: DT, drug therapy  
Retina: DE, drug effects  
Tacrolimus: TU, therapeutic use  
**Thalidomide: TU, therapeutic use**  
Wegener's Granulomatosis: DT, drug therapy  
CAS REGISTRY NO.: 109581-93-3 (Tacrolimus); 118-42-3 (Hydroxychloroquine);  
4291-63-8 (Cladribine); 446-86-6 (Azathioprine); 50-18-0  
(Cyclophosphamide); 50-35-1 (Thalidomide); 59-05-2  
(Methotrexate); 59865-13-3 (Cyclosporine)

CHEMICAL NAME: 0 (Immunosuppressive Agents)

L127 ANSWER 5 OF 9 MEDLINE on STN  
ACCESSION NUMBER: 95229221 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7713571  
TITLE: Cytokine regulation of disease progression in leprosy and tuberculosis.  
AUTHOR: Kaplan G  
CORPORATE SOURCE: Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York.  
SOURCE: Immunobiology, (1994 Oct) 191 (4-5) 564-8.  
Journal code: 8002742. ISSN: 0171-2985.  
PUB. COUNTRY: GERMANY: Germany, Federal Republic of  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS  
ENTRY MONTH: 199505  
ENTRY DATE: Entered STN: 19950524  
Last Updated on STN: 19970203  
Entered Medline: 19950512

## ABSTRACT:

Studies in our laboratory have focussed on the role of cytokines in the regulation of the cellular immune response and disease progression in two important mycobacterial infection of man, namely leprosy and tuberculosis. Our studies in leprosy have involved the use of key regulatory cytokines such as IFN-gamma in the modulation of the cellular response of infected patients. We have investigated the effect of intradermal administration of low dose IFN-gamma on the lesions of anergic lepromatous patients and have reported an accelerated bacillary clearance from the skin. This was associated with the local accumulation of mononuclear cells and killing of infected macrophages. However, IFN-gamma administration also resulted in the induction of erythema nodosum leprosum, a toxic syndrome associated with excess TNF-alpha production. Both the toxic symptoms and the high levels of TNF-alpha production could be inhibited by thalidomide treatment, a drug we have shown reduces the half life of TNF-alpha mRNA. In preliminary clinical trials in tuberculosis patients we have attempted to use thalidomide to reduce TNF-alpha production and toxicities. These results are discussed.

CONTROLLED TERM: Check Tags: Human  
AIDS-Related Opportunistic Infections: CO, complications  
AIDS-Related Opportunistic Infections: DT, drug therapy  
\*Cytokines: PH, physiology  
Erythema Nodosum: ET, etiology  
Erythema Nodosum: PC, prevention & control  
HIV-1  
Immunity, Cellular  
Injections, Intradermal  
Interferon-gamma, Recombinant: AD, administration & dosage  
**Interferon-gamma, Recombinant: AE, adverse effects**  
\*Leprosy, Lepromatous: ET, etiology  
Leprosy, Lepromatous: TH, therapy  
**Thalidomide: AD, administration & dosage**  
Tuberculosis: CO, complications  
Tuberculosis: DT, drug therapy  
\*Tuberculosis: ET, etiology  
Tumor Necrosis Factor: AI, antagonists & inhibitors  
Tumor Necrosis Factor: BI, biosynthesis  
CAS REGISTRY NO.: 50-35-1 (Thalidomide)  
CHEMICAL NAME: 0 (Cytokines); 0 (Interferon-gamma, Recombinant); 0 (Tumor Necrosis Factor)

L127 ANSWER 6 OF 9 MEDLINE on STN  
ACCESSION NUMBER: 92268822 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 1588290  
TITLE: Prolonged treatment with recombinant interferon gamma induces erythema nodosum leprosum in lepromatous leprosy patients.  
AUTHOR: Sampaio E P; Moreira A L; Sarno E N; Malta A M; Kaplan G  
CORPORATE SOURCE: Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York, New York 10021.  
CONTRACT NUMBER: AI-22616 (NIAID)  
SOURCE: Journal of experimental medicine, (1992 Jun 1) 175 (6) 1729-37.  
Journal code: 2985109R. ISSN: 0022-1007.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199206  
ENTRY DATE: Entered STN: 19920710  
Last Updated on STN: 19920710  
Entered Medline: 19920623

## ABSTRACT:

10 patients with borderline and lepromatous leprosy were selected for a prolonged trial with recombinant interferon gamma (rIFN-gamma). Patients received 30 micrograms intradermally for six injections over a 9-d period, and then either 100 micrograms intradermally every 1 mo for 10 mo or every 2 wk for 5 mo (total, 1.2 mg). Erythema nodosum leprosum (ENL) was induced in 60% of the patients within 6-7 mo, as compared with an incidence of 15% per year with multiple drug therapy alone. The mean whole-body reduction in bacterial index over the first 6 mo was 0.9 log units. Cutaneous induration at the intradermal injection sites of greater than or equal to 15 mm predicted the development of a subsequent reactional state. Monocytes obtained from patients receiving the lymphokine demonstrated an increased respiratory burst and a 2.5-5.1-fold increase in tumor necrosis factor alpha (TNF-alpha) secretion in response to agonists. Patients in ENL had an even higher release of TNF-alpha from monocytes as well as high levels of TNF-alpha in the plasma (mean, 2,000 pg/ml). Thalidomide therapy was required to treat the systemic manifestations of ENL. Control of toxic symptoms with thalidomide was associated with a 50-80% reduction in agonist-stimulated monocyte TNF-alpha secretion. IFN-gamma enhanced the monocyte release of TNF-alpha by 3-7.5-fold (agonist dependent) when added to patient's cells in vitro, and this could be suppressed by the in vitro addition of 10 micrograms/ml of thalidomide.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

\*Erythema Nodosum: CI, chemically induced

Erythema Nodosum: DT, drug therapy

Erythema Nodosum: PA, pathology

\*Interferon-gamma, Recombinant: AE, adverse effects

Interferon-gamma, Recombinant: TU, therapeutic use

Leprosy, Borderline: PA, pathology

\*Leprosy, Borderline: TH, therapy

\*Leprosy, Lepromatous: CI, chemically induced

Leprosy, Lepromatous: PA, pathology

\*Leprosy, Lepromatous: TH, therapy

Monocytes: DE, drug effects

Monocytes: PH, physiology

Skin: PA, pathology

\*Thalidomide: TU, therapeutic use

Time Factors

Tumor Necrosis Factor: BI, biosynthesis

CAS REGISTRY NO.: 50-35-1 (Thalidomide)

CHEMICAL NAME: 0 (Interferon-gamma, Recombinant); 0 (Tumor Necrosis Factor)

L127 ANSWER 7 OF 9

MEDLINE on STN

ACCESSION NUMBER: 66169692 MEDLINE

DOCUMENT NUMBER: PubMed ID: 5887938

TITLE: [Use of the imide of N-phthalylglutamic acid (thalidomide) in the symptomatic therapy of vomiting of many patients with malignant neoplasms or caused by the administration of mechlorethamine HCl].

L'impiego dell'imide dell'acido N-ftalilglutammico (thalidomide) nella terapia sintomatica del vomito di molti pazienti affetti da neoplasie maligne o causato dalla somministrazione di cloridato di mecloretamina.

AUTHOR: Traldi A; Vaccari G L; Davoli G

SOURCE: Il Cancro, (1965) 18 (4) 336-41.

Journal code: 0421125. ISSN: 0008-5480.

PUB. COUNTRY: Italy

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: Italian  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 196610  
ENTRY DATE: Entered STN: 19900101  
Last Updated on STN: 19900101  
Entered Medline: 19661016  
CONTROLLED TERM: Check Tags: Female; Human; Male  
Adolescent  
Adult  
Aged  
Child  
\*Mechlorethamine: AE, adverse effects  
Middle Aged  
Neoplasms: CO, complications  
\*Thalidomide: TU, therapeutic use  
\*Vomiting: DT, drug therapy  
CAS REGISTRY NO.: 50-35-1 (Thalidomide); 51-75-2 (Mechlorethamine)  
L127 ANSWER 8 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN  
ACCESSION NUMBER: 2004116291 EMBASE  
TITLE: Novel therapies in prostate cancer.  
AUTHOR: Turkeri L.N.  
CORPORATE SOURCE: L.N. Turkeri, Department of Urology, School of Medicine,  
Marmara University, Istanbul, Turkey. turkeri@marun.edu.tr  
SOURCE: European Urology, Supplements, (2004) 3/3 (63-69).  
Refs: 62  
ISSN: 1569-9056 CODEN: EUSUAU  
PUBLISHER IDENT.: S 1569-9056(04)00037-5  
COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
028 Urology and Nephrology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
CONTROLLED TERM: Medical Descriptors:  
\*prostate cancer: DT, drug therapy  
\*cancer therapy  
\*cancer immunotherapy  
\*gene therapy  
drug efficacy  
dendritic cell  
fever: SI, side effect  
adoptive immunotherapy  
cancer survival  
toxicity: SI, side effect  
tumor suppressor gene  
adenovirus vector  
side effect: SI, side effect  
genetic transfection  
suicide gene therapy  
gene expression  
immunohistochemistry  
rhinitis: SI, side effect  
headache: SI, side effect  
asthenia: SI, side effect  
peripheral edema: SI, side effect  
human

clinical trial  
conference paper  
priority journal  
Drug Descriptors:  
\*granulocyte macrophage colony stimulating factor: CT,  
clinical trial  
\*granulocyte macrophage colony stimulating factor: DO, drug  
dose  
\*granulocyte macrophage colony stimulating factor: DT, drug  
therapy  
\*granulocyte macrophage colony stimulating factor: PD,  
pharmacology  
\*granulocyte macrophage colony stimulating factor: SC,  
subcutaneous drug administration  
\*antisense oligonucleotide: AE, adverse drug reaction  
\*antisense oligonucleotide: CT, clinical trial  
\*antisense oligonucleotide: CB, drug combination  
\*antisense oligonucleotide: DO, drug dose  
\*antisense oligonucleotide: DT, drug therapy  
\*antisense oligonucleotide: PD, pharmacology  
\*cetuximab: CT, clinical trial  
\*cetuximab: CB, drug combination  
\*cetuximab: DT, drug therapy  
\*cetuximab: PD, pharmacology  
    **\*gefitinib: AE, adverse drug reaction**  
\*gefitinib: CT, clinical trial  
\*gefitinib: CB, drug combination  
\*gefitinib: DO, drug dose  
\*gefitinib: DT, drug therapy  
\*gefitinib: PD, pharmacology  
\*thalidomide: CT, clinical trial  
\*thalidomide: CB, drug combination  
    **\*thalidomide: DO, drug dose**  
    **\*thalidomide: IT, drug interaction**  
    **\*thalidomide: DT, drug therapy**  
    **\*thalidomide: PD, pharmacology**  
prostate specific membrane antigen: CT, clinical trial  
prostate specific membrane antigen: DT, drug therapy  
prostate specific membrane antigen: PD, pharmacology  
HLA A2 antigen: CT, clinical trial  
HLA A2 antigen: DT, drug therapy  
HLA A2 antigen: PD, pharmacology  
acid phosphatase prostate isoenzyme: AE, adverse drug  
reaction  
acid phosphatase prostate isoenzyme: CT, clinical trial  
acid phosphatase prostate isoenzyme: DT, drug therapy  
acid phosphatase prostate isoenzyme: PD, pharmacology  
dcvax: AE, adverse drug reaction  
dcvax: CT, clinical trial  
dcvax: DT, drug therapy  
dcvax: DL, intradermal drug administration  
immunomodulating agent: AE, adverse drug reaction  
immunomodulating agent: CT, clinical trial  
immunomodulating agent: DT, drug therapy  
immunomodulating agent: DL, intradermal drug administration  
prostate specific antigen: EC, endogenous compound  
protein p53: AE, adverse drug reaction  
protein p53: CT, clinical trial  
protein p53: AD, drug administration  
protein p53: DT, drug therapy  
ganciclovir  
aciclovir

valaciclovir

**mitoxantrone: AE, adverse drug reaction**

mitoxantrone: CT, clinical trial

mitoxantrone: CB, drug combination

mitoxantrone: DO, drug dose

mitoxantrone: DT, drug therapy

mitoxantrone: PD, pharmacology

antisense phosphorodiamidate morpholino oligomer: AE, adverse drug reaction

antisense phosphorodiamidate morpholino oligomer: CT, clinical trial

antisense phosphorodiamidate morpholino oligomer: DT, drug therapy

antisense phosphorodiamidate morpholino oligomer: IV, intravenous drug administration

antisense phosphorodiamidate morpholino oligomer: PD, pharmacology

**antineoplastic agent: AE, adverse drug reaction**

antineoplastic agent: CT, clinical trial

antineoplastic agent: DT, drug therapy

antineoplastic agent: IV, intravenous drug administration

antineoplastic agent: PD, pharmacology

epidermal growth factor receptor 2: EC, endogenous compound

doxorubicin: CT, clinical trial

doxorubicin: CB, drug combination

doxorubicin: DT, drug therapy

**docetaxel: AE, adverse drug reaction**

docetaxel: CT, clinical trial

docetaxel: CB, drug combination

docetaxel: DO, drug dose

docetaxel: IT, drug interaction

docetaxel: DT, drug therapy

**estramustine phosphate: AE, adverse drug reaction**

estramustine phosphate: CT, clinical trial

estramustine phosphate: CB, drug combination

estramustine phosphate: DT, drug therapy

prednisone: CT, clinical trial

prednisone: CB, drug combination

prednisone: DT, drug therapy

lapatinib: PD, pharmacology

endothelin 1: PD, pharmacology

atrasentan: AE, adverse drug reaction

atrasentan: CT, clinical trial

atrasentan: DO, drug dose

atrasentan: DT, drug therapy

atrasentan: PD, pharmacology

17 allylamino 17 demethoxygeldanamycin: PD, pharmacology

geldanamycin: PD, pharmacology

trastuzumab: PD, pharmacology

placebo

unclassified drug

provenge

avi 4126

CAS REGISTRY NO.:

(cetuximab) 205923-56-4; (gefitinib) 184475-35-2,

184475-55-6, 184475-56-7; (thalidomide) 50-35-1;

(ganciclovir) 82410-32-0; (aciclovir) 59277-89-3;

(valaciclovir) 124832-26-4; (mitoxantrone) 65271-80-9,

70476-82-3; (epidermal growth factor receptor 2)

137632-09-8; (doxorubicin) 23214-92-8, 25316-40-9;

(docetaxel) 114977-28-5; (estramustine phosphate)

4891-15-0; (prednisone) 53-03-2; (lapatinib) 388082-78-8,

437755-78-7; (atrasentan) 173864-34-1, 173937-91-2,



195733-43-8; (geldanamycin) 30562-34-6; (trastuzumab)  
180288-69-1

CHEMICAL NAME: (1) Dcvax; Provenge; Avi 4126; Iressa; Gw 572016; Abt 627;  
Herceptin

COMPANY NAME: (1) Northwest

L127 ANSWER 9 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2001079608 EMBASE

TITLE: [Thalidomide prevents severe **side-effect**  
of crinotecan].  
THALIDOMIDE VOORKOMT ERNSTIGE BIJWERKING VAN IRINOTECAN.

AUTHOR: Gebhardt D.O.E.

SOURCE: Pharmaceutisch Weekblad, (23 Feb 2001) 136/8 (271).  
Refs: 6  
ISSN: 0031-6911 CODEN: PHWEAW

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Note

FILE SEGMENT: 009 Surgery  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: Dutch

CONTROLLED TERM: Medical Descriptors:  
\*graft versus host reaction: DT, drug therapy  
lupus erythematosus: SI, side effect  
drug antagonism  
human  
note  
Drug Descriptors:  
\*thalidomide: DO, drug dose  
\*thalidomide: IT, drug interaction  
\*thalidomide: DT, drug therapy  
\*irinotecan: AE, adverse drug reaction  
\*irinotecan: DO, drug dose  
\*irinotecan: IT, drug interaction  
\*irinotecan: DT, drug therapy

CAS REGISTRY NO.: (thalidomide) 50-35-1; (irinotecan) 100286-90-6

=> fil medl; d que 145

FILE 'MEDLINE' ENTERED AT 13:15:35 ON 20 JUL 2004

FILE LAST UPDATED: 17 JUL 2004 (20040717/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLD MEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L37 2628 SEA FILE=MEDLINE ABB=ON THALIDOMIDE/CT  
L44 29987 SEA FILE=MEDLINE ABB=ON DIARRHEA+NT/CT  
L45 9 SEA FILE=MEDLINE ABB=ON L37 AND L44

=> fil embase; d que 174; fil capl; d que nos 1107; dup rem 145,1107,174

FILE 'EMBASE' ENTERED AT 13:16:21 ON 20 JUL 2004

COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE COVERS 1974 TO 15 Jul 2004 (20040715/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L67 5431 SEA FILE=EMBASE ABB=ON THALIDOMIDE/CT OR THALIDOMIDE DERIVATIV  
E/CT  
L68 54141 SEA FILE=EMBASE ABB=ON DIARRHEA+NT/CT  
L70 5286 SEA FILE=EMBASE ABB=ON L68 (L) (DT OR PC)/CT  
L71 3239 SEA FILE=EMBASE ABB=ON L70/MAJ  
L72 3299 SEA FILE=EMBASE ABB=ON L67 (L) (AD OR DO OR PD OR PK OR DT)/CT  
L74 8 SEA FILE=EMBASE ABB=ON L71 AND L72

FILE 'CAPLUS' ENTERED AT 13:16:21 ON 20 JUL 2004

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 20 Jul 2004 VOL 141 ISS 4

FILE LAST UPDATED: 19 Jul 2004 (20040719/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L6 STR  
L8 66 SEA FILE=REGISTRY FAM FUL L6  
L104 1669 SEA FILE=CAPLUS ABB=ON L8  
L105 4927 SEA FILE=CAPLUS ABB=ON DIARRHEA/CT  
L106 725 SEA FILE=CAPLUS ABB=ON ANTIDIARRHEALS/CT  
L107 14 SEA FILE=CAPLUS ABB=ON L104 AND (L105 OR L106)

FILE 'MEDLINE' ENTERED AT 13:16:22 ON 20 JUL 2004

FILE 'CAPLUS' ENTERED AT 13:16:22 ON 20 JUL 2004  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 13:16:22 ON 20 JUL 2004  
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.  
PROCESSING COMPLETED FOR L45  
PROCESSING COMPLETED FOR L107  
PROCESSING COMPLETED FOR L74  
L128 30 DUP REM L45 L107 L74 (1 DUPLICATE REMOVED)  
ANSWERS '1-9' FROM FILE MEDLINE  
ANSWERS '10-22' FROM FILE CAPLUS  
ANSWERS '23-30' FROM FILE EMBASE

=> d ibib ed ab hitrn 1-30

L128 ANSWER 1 OF 30 MEDLINE on STN DUPLICATE 1  
ACCESSION NUMBER: 97322018 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9178672  
TITLE: Thalidomide: a novel therapy for microsporidiosis.  
COMMENT: Erratum in: Gastroenterology 1997 Sep;113(3):1054  
AUTHOR: Sharpstone D; Rowbottom A; Francis N; Tovey G; Ellis D;  
Barrett M; Gazzard B  
CORPORATE SOURCE: Department of HIV/GUM, Chelsea and Westminster Hospital,  
London, England.  
SOURCE: Gastroenterology, (1997 Jun) 112 (6) 1823-9.  
Journal code: 0374630. ISSN: 0016-5085.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS  
ENTRY MONTH: 199707  
ENTRY DATE: Entered STN: 19970805  
Last Updated on STN: 19990129  
Entered Medline: 19970721  
ED Entered STN: 19970805  
Last Updated on STN: 19990129  
Entered Medline: 19970721  
AB BACKGROUND & AIMS: Microsporidiosis is a common cause of chronic diarrhea  
in human immunodeficiency virus (HIV)-seropositive individuals and often  
does not respond to treatment. Fecal tumor necrosis factor alpha

(TNF-alpha) is elevated in microsporidiosis; therefore, thalidomide, an anti-TNF-alpha agent, was used as therapy. METHODS: Eighteen subjects with chronic diarrhea caused by Enterocytozoon bienersi that had not responded symptomatically to albendazole and 1 untreated subject with Encephalitozoon intestinalis received 1 month of thalidomide, 100 mg nocte. Clinical response was assessed by stool frequency and body weight, histological response by light microscopy with villus height/crypt depth ratios and electron microscopy, and immunologic response by fecal TNF-alpha level. RESULTS: Seven subjects with chronic diarrhea due to E. bienersi had a complete clinical response, and 3 had a partial response to thalidomide. There was a significant decrease in stool frequency from 5.3 to 3.1 per day ( $P = 0.001$ ), and weight increased significantly by 1.2 kg ( $P < 0.02$ ). Thalidomide significantly increased the villus height/crypt depth ratio (1.95 to 2.07;  $P = 0.045$ ) and number of abnormal forms of microsporidia ( $P < 0.01$ ). Fecal TNF-alpha level nonsignificantly decreased from 17.9 to 8.9 U/mL. There was apparent disruption of all stages of the life cycle of E. intestinalis. CONCLUSIONS: Thalidomide may be an effective therapy for diarrhea and weight loss from E. bienersi.

L128 ANSWER 2 OF 30 MEDLINE on STN  
ACCESSION NUMBER: 2002298600 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12040298  
TITLE: Thalidomide and irinotecan-associated diarrhea.  
AUTHOR: Tchekmedyian N Simon  
SOURCE: American journal of clinical oncology : official  
publication of the American Radium Society, (2002 Jun) 25  
(3) 324.  
Journal code: 8207754. ISSN: 0277-3732.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CASE REPORTS)  
Letter  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200206  
ENTRY DATE: Entered STN: 20020602  
Last Updated on STN: 20020628  
Entered Medline: 20020627  
ED Entered STN: 20020602  
Last Updated on STN: 20020628  
Entered Medline: 20020627

L128 ANSWER 3 OF 30 MEDLINE on STN  
ACCESSION NUMBER: 2000414475 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10950238  
TITLE: Effect of thalidomide on gastrointestinal toxic effects of  
irinotecan.  
AUTHOR: Govindarajan R; Heaton K M; Broadwater R; Zeitlin A; Lang N  
P; Hauer-Jensen M  
SOURCE: Lancet, (2000 Aug 12) 356 (9229) 566-7.  
Journal code: 2985213R. ISSN: 0140-6736.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Letter  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS  
ENTRY MONTH: 200008  
ENTRY DATE: Entered STN: 20000907  
Last Updated on STN: 20000907  
Entered Medline: 20000829  
ED Entered STN: 20000907  
Last Updated on STN: 20000907  
Entered Medline: 20000829

AB Irinotecan is the only accepted second-line treatment for colorectal cancer in the USA. Doses are, however, frequently limited by associated late-onset diarrhoea. Thalidomide has antiangiogenic and immunomodulatory properties and is being investigated as an antineoplastic. We did a pilot study of combination therapy with thalidomide and irinotecan for metastatic colorectal cancer. In an interim analysis of nine patients, thalidomide had almost eliminated the dose-limiting gastrointestinal toxic effects of irinotecan, especially diarrhoea and nausea (each  $p < 0.0001$ ), and eight of nine patients were able to complete the chemotherapy course.

L128 ANSWER 4 OF 30 MEDLINE on STN  
ACCESSION NUMBER: 1998060704 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9399783  
TITLE: Thalidomide for AIDS diarrhea?.  
AUTHOR: Surawicz C M  
CORPORATE SOURCE: University of Washington, Seattle, USA.  
SOURCE: American journal of gastroenterology, (1997 Dec) 92 (12)  
2312-3.  
Journal code: 0421030. ISSN: 0002-9270.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; AIDS  
ENTRY MONTH: 199712  
ENTRY DATE: Entered STN: 19980116  
Last Updated on STN: 19980116  
Entered Medline: 19971229  
ED Entered STN: 19980116  
Last Updated on STN: 19980116  
Entered Medline: 19971229

L128 ANSWER 5 OF 30 MEDLINE on STN  
ACCESSION NUMBER: 2001281314 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11364706  
TITLE: Thalidomide shows benefit for microsporidial diarrhea.  
AUTHOR: Bartnof H S  
SOURCE: BETA bulletin of experimental treatments for AIDS : a  
publication of the San Francisco AIDS foundation, (1997  
Sep) 51-2.  
Journal code: 9113964. ISSN: 1058-708X.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (NEWSPAPER ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: AIDS  
ENTRY MONTH: 199710  
ENTRY DATE: Entered STN: 20010529  
Last Updated on STN: 20020222  
Entered Medline: 19971007  
ED Entered STN: 20010529  
Last Updated on STN: 20020222  
Entered Medline: 19971007

AB Chronic diarrhea is a common symptom in HIV-positive persons, much of it due to microsporidia infections. Several drugs are used to treat diarrhea, but the infection is frequently not cleared and the symptoms recur. Thalidomide (Synovir) has been tested in eighteen patients who did not respond to other therapies. Thirty-eight percent achieved complete clinical remission, significant weight gain, and improved results of intestinal biopsies. Thalidomide is an experimental drug currently used for oral aphthous ulcers and wasting syndrome, and is the same drug associated with severe fetal abnormalities in the 1960s.

L128 ANSWER 6 OF 30 MEDLINE on STN

ACCESSION NUMBER: 2001280144 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11363536  
TITLE: Thalidomide used to treat chronic diarrhea in HIV-positive patients.  
AUTHOR: Anonymous  
SOURCE: Journal of the International Association of Physicians in AIDS Care, (1996 May) 2 (5) 51.  
Journal code: 9508185. ISSN: 1081-454X.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
(NEWSPAPER ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: AIDS  
ENTRY MONTH: 199607  
ENTRY DATE: Entered STN: 20010529  
Last Updated on STN: 20020222  
Entered Medline: 19960702

ED Entered STN: 20010529  
Last Updated on STN: 20020222  
Entered Medline: 19960702

AB Celgene Corporation initiated a phase II safety and efficacy trial for Synovir (thalidomide) in the treatment of chronic intractable diarrhea in HIV-positive patients. The double-blind trial will involve 120 patients over 28 days of therapy. The primary endpoint is the reduction in the occurrence of diarrhea. Celgene is now dispensing Synovir in the United States for treatment of cachexia under an FDA-approved expanded use protocol.

L128 ANSWER 7 OF 30 MEDLINE on STN  
ACCESSION NUMBER: 2001280321 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11363713  
TITLE: Thalidomide for diarrhea.  
AUTHOR: Anonymous  
SOURCE: GMHC treatment issues : Gay Men's Health Crisis newsletter of experimental AIDS therapies, (1996 Apr) 10 (4) 9.  
Journal code: 9509489. ISSN: 1077-1824.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CLINICAL TRIAL)  
(NEWSPAPER ARTICLE)  
(RANDOMIZED CONTROLLED TRIAL)  
LANGUAGE: English  
FILE SEGMENT: AIDS  
ENTRY MONTH: 199608  
ENTRY DATE: Entered STN: 20010529  
Last Updated on STN: 20020222  
Entered Medline: 19960814

ED Entered STN: 20010529  
Last Updated on STN: 20020222  
Entered Medline: 19960814

AB A phase II trial is beginning using thalidomide as a treatment for chronic diarrhea in HIV-infected patients. The 28-day trial will randomize 120 patients to placebo or 100 mg thalidomide daily. Areas monitored will include changes in body weight, quality of life, and tumor necrosis factor (TNF) in small bowel tissue.

L128 ANSWER 8 OF 30 MEDLINE on STN  
ACCESSION NUMBER: 95391183 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7662213  
TITLE: The treatment of microsporidial diarrhoea with thalidomide.  
AUTHOR: Sharpstone D; Rowbottom A; Nelson M; Gazzard B  
SOURCE: AIDS (London, England), (1995 Jun) 9 (6) 658-9.  
Journal code: 8710219. ISSN: 0269-9370.

PUB. COUNTRY: United States  
 DOCUMENT TYPE: Letter  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals; AIDS  
 ENTRY MONTH: 199510  
 ENTRY DATE: Entered STN: 19951020  
 Last Updated on STN: 19951020  
 Entered Medline: 19951006

ED Entered STN: 19951020  
 Last Updated on STN: 19951020  
 Entered Medline: 19951006

L128 ANSWER 9 OF 30 MEDLINE on STN  
 ACCESSION NUMBER: 72061703 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 4399536  
 TITLE: Several problems of drug therapy in pregnancy.  
 AUTHOR: Sugiyama Y  
 SOURCE: Iryo, (1971 Sep) 25 (9) 646-50. Ref: 11  
 Journal code: 0413672. ISSN: 0021-1699.

PUB. COUNTRY: Japan  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 LANGUAGE: Japanese  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 197202  
 ENTRY DATE: Entered STN: 19900310  
 Last Updated on STN: 19970203  
 Entered Medline: 19720216

ED Entered STN: 19900310  
 Last Updated on STN: 19970203  
 Entered Medline: 19720216

L128 ANSWER 10 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2003:319266 CAPLUS  
 DOCUMENT NUMBER: 138:343857  
 TITLE: Pharmaceutical formulations and systems for improved  
 absorption and multistage release of active agents  
 INVENTOR(S): Chen, Feng-Jing; Venkateshwaran, Srinivasan; Krill,  
 Steven L.; Patel, Mahesh V.  
 PATENT ASSIGNEE(S): USA  
 SOURCE: U.S. Pat. Appl. Publ., 55 pp., Cont.-in-part of U.S.  
 Ser. No. 898,553.  
 CODEN: USXXCO  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 12  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003077297	A1	20030424	US 2002-74687	20020211
US 6294192	B1	20010925	US 1999-258654	19990226
US 6267985	B1	20010731	US 1999-345615	19990630
US 6248363	B1	20010619	US 1999-447690	19991123
US 2003064097	A1	20030403	US 2001-800593	20010306
US 6569463	B2	20030527		
US 2002032171	A1	20020314	US 2001-877541	20010608
US 6761903	B2	20040713		
US 2002012680	A1	20020131	US 2001-898553	20010702
US 6451339	B2	20020917		
WO 2003068186	A1	20030821	WO 2003-US4195	20030211

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,  
 PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,  
 UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
 TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,  
 NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
 ML, MR, NE, SN, TD, TG

## PRIORITY APPLN. INFO.:

US 1999-258654	A1 19990226
US 1999-345615	A2 19990630
US 1999-447690	A3 19991123
US 2001-800593	A2 20010306
US 2001-877541	A2 20010608
US 2001-898553	A2 20010702
US 1999-375636	A2 19990817
US 2000-751968	A2 20001229
US 2002-74687	A 20020211

ED Entered STN: 25 Apr 2003

AB The present invention pertains to pharmaceutical formulations and systems for delivery of active agents, wherein a first fraction of an active agent is suspended in a vehicle and a second fraction of active agent is solubilized in the vehicle, with the suspended fraction representing about 5 wt. % to about 80 wt. % of the active agent and the second fraction representing about 20 wt. % to about 95 wt. % of the active agent. One or more addnl. active agents, which may be fully solubilized, partially solubilized, or suspended, may also be present. The first and second fractions of the active agent may or may not have different release profiles. Generally, a significant fraction of the solubilized drug will release rapidly, providing for rapid onset, while the suspended drug may be formulated for delayed and/or sustained release. A pharmaceutical suspension contained isotretinoin 40, soybean oil 200, Maisine 35-1 100, and Lutrol F68 100 mg.

IT 50-35-1, Thalidomide

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (pharmaceutical formulations and systems for improved absorption and multistage release of active agents)

L128 ANSWER 11 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:736019 CAPLUS

DOCUMENT NUMBER: 137:242162

TITLE: Combinations of an antidiarrheal agent and an epothelione derivative for the treatment of a proliferative disease

INVENTOR(S): Rothermel, John David; Schran, Horst F.; Greeley, Diane; Chen, TianLing

PATENT ASSIGNEE(S): Novartis A.-G., USA; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.

SOURCE: PCT Int. Appl., 21 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074042	A2	20020926	WO 2002-EP2977	20020318
WO 2002074042	A3	20030227		

W: AT, AU, BG, CH, CN, CR, DE, DK, HU, ID, IS, JP, LK, LT, MN, MX,  
 NZ, TT, UA, SK, TN, UA, US, RU, TJ, TM



RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, IE, LU, MC, NL, PT, SE, TR  
EP 1372650 A2 20040102 EP 2002-719992 20020318  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
BR 2002008142 A 20040302 BR 2002-8142 20020318  
JP 2004519493 T2 20040702 JP 2002-572770 20020318  
NO 2003004094 A 20030915 NO 2003-4094 20030915  
US 2004092478 A1 20040513 US 2003-471904 20030915  
PRIORITY APPLN. INFO.: US 2001-277153P P 20010319  
US 2001-277207P P 20010320  
WO 2002-EP2977 W 20020318

OTHER SOURCE(S): MARPAT 137:242162

ED Entered STN: 27 Sep 2002

AB Epothilone derivs. are co-administered with an antidiarrheal agent, e.g.,  
a dipeptidyl peptidase IV inhibitor, in the treatment of a proliferative  
disease.

IT 50-35-1, Thalidomide

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(antidiarrheal agent-epothelione deriv. combination for treatment of  
proliferative disease)

L128 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:521462 CAPLUS

DOCUMENT NUMBER: 137:88442

TITLE: Incensole and furanogermacrens and compounds in  
treatment for inhibiting neoplastic lesions and  
microorganisms

INVENTOR(S): Shanahan-Pendergast, Elisabeth

PATENT ASSIGNEE(S): Ire.

SOURCE: PCT Int. Appl., 68 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE1	20020102
WO 2002053138	A3	20020919		
W:	AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG			
EP 1351678	A2	20031015	EP 2002-727007	20020102
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
US 2004092583	A1	20040513	US 2004-250535	20040102
PRIORITY APPLN. INFO.:			IE 2001-2	A 20010102
			WO 2002-IE1	W 20020102

OTHER SOURCE(S): MARPAT 137:88442

ED Entered STN: 12 Jul 2002

AB The invention discloses the use of incensole and/or furanogermacrens,  
derivs. metabolites and precursors thereof in the treatment of neoplasia,  
particularly resistant neoplasia and immunodysregulatory disorders. These  
compds. can be administered alone or in combination with conventional  
chemotherapeutic, antiviral, antiparasite agents, radiation and/or  
surgery. Incensole and furanogermacren and their mixt. showed antitumor  
activity against various human carcinomas and melanomas and antimicrobial  
activity against Staphylococcus aureus and Enterococcus faecalis.

IT 50-35-1, Thalidomide

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(pharmaceutical formulation further including; incensole and furanogermacrens and compds. as antitumor and antimicrobial agents)

L128 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:428706 CAPLUS

DOCUMENT NUMBER: 137:702

TITLE: Compositions and methods using temozolomide and thalidomide for the treatment of cancer

INVENTOR(S): Hwu, Wen Jen

PATENT ASSIGNEE(S): Memorial Sloan-Kettering Cancer Center, USA

SOURCE: PCT Int. Appl., 55 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002043720	A2	20020606	WO 2001-US47674	20011203
WO 2002043720	A3	20020912		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2002128228	A1	20020912	US 2001-1281	20011130
AU 2002026069	A5	20020611	AU 2002-26069	20011203
EP 1343500	A2	20030917	EP 2001-995489	20011203
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			

PRIORITY APPLN. INFO.: US 2000-250130P P 20001201  
WO 2001-US47674 W 20011203

ED Entered STN: 07 Jun 2002

AB The invention provides compns. comprising temozolomide and thalidomide which can be used in the treatment of prevention of cancer, in particular malignant melanoma, cancer of the skin, s.c. tissue, lymph nodes, brain, lung, liver, bone, intestine, colon, heart, pancreas, adrenals, kidney, prostate, breast, colorectal, or a combination thereof. A particular compn. comprises temozolomide, or a pharmaceutically acceptable salt, solvate, or clathrate thereof; and thalidomide, or a pharmaceutically acceptable salt, solvate, or clathrate thereof. The invention also provides methods of treating or preventing cancer, in particular malignant melanoma, cancer of the skin, s.c. tissue, lymph nodes, brain, lung, liver, bone intestine, colon, heart, pancreas, adrenals, kidney, prostate, breast, colorectal, or a combination thereof, which comprise the administration of temozolomide and thalidomide and another anti-cancer drug to a patient in need of such treatment or prevention. The invention further provides methods of reducing or avoiding adverse side effects assocd. with the administration of cancer chemotherapy or radiation therapy which comprise the administration of temozolomide and thalidomide to a patient in need of such redn. or avoidance.

IT 50-35-1, Thalidomide 50-35-1D, Thalidomide, prodrugs

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(temozolomide and thalidomide for treatment of cancer)

L128 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:718875 CAPLUS

DOCUMENT NUMBER: 137:272675

TITLE: Thalidomide: an old drug with new clinical applications.

AUTHOR(S): Baidas, Said; Tfayli, Arafat; Bhargava, Pankaj

CORPORATE SOURCE: Lombardi Cancer Center, Georgetown University

Hospital, Washington, DC, 20007, USA

SOURCE: Cancer Investigation (2002), 20(5 &amp; 6), 835-848

CODEN: CINVD7; ISSN: 0735-7907

PUBLISHER: Marcel Dekker, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 23 Sep 2002

AB A review. Currently thalidomide is entering clin. trials in a wide variety of diseases ranging from cancer to autoimmune and inflammatory conditions. This wide range of possible applications requires further search into the mechanism of thalidomide activities. Thalidomide as a single agent has shown some activity in a variety of solid tumors, but the most impressive activity has been obsd. in MM. Further clin. trials are required to clarify the role of thalidomide in combination with other chemotherapy agents, other immune modulators, or other anti-angiogenesis agents in the treatment of cancer. The teratogenic activity of thalidomide will continue to pose a real threat to the widespread clin. use of this drug.

IT 50-35-1, Thalidomide

RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thalidomide: an old drug with new clin. applications for humans)

REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L128 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:949420 CAPLUS

DOCUMENT NUMBER: 138:19261

TITLE: Thalidomide in chronic graft-versus-host disease after stem cell transplantation: effects on quality of life

AUTHOR(S): Miller, Steve; Sharda, Shalini; Rodrigue, James;

Mehta, Paulette

CORPORATE SOURCE: Departments of Pediatrics and Internal Medicine and

the Bone Marrow Transplant Program, University of

Florida College of Medicine, Gainesville, FL, USA

SOURCE: International Journal of Hematology (2002), 76(4),

365-369

CODEN: IJHEEY; ISSN: 0925-5710

PUBLISHER: Carden Jennings Publishing

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 16 Dec 2002

AB Thalidomide is being increasingly used after stem cell transplantation as immunosuppression for patients with chronic graft-vs.-host disease, as well as for antiangiogenesis effects in patients with multiple myeloma, brain tumors, leukemia, or other malignancies. The goal of this study was to det. if thalidomide improved the quality of life by virtue of its assocd. sleep-promoting, anxiety-reducing, antiwasting, and antidiarrheal effects. We therefore studied 28 patients with resistant chronic graft-vs.-host disease who were treated with thalidomide (13 patients) or other immunosuppressive drugs (15) and compared them with healthy control subjects (16). All patients completed quality-of-life questionnaires

prospectively before beginning regimens of thalidomide or other immunosuppressive drugs and completed similar questionnaires at 3- and 6-mo intervals thereafter. The Transplant Symptom Frequency score was similar for healthy control subjects and both groups of patients with chronic graft-vs.-host disease, regardless of whether they had received thalidomide or not. Quality of sleep was equally poor in patients who received or did not receive thalidomide. The most common complaint of patients with chronic graft-vs.-host disease was fatigue, followed in frequency by overeating. The control group had similar concerns. This pilot study suggests that patients with chronic graft-vs.-host disease have a quality of life similar to that of their health care workers, regardless of whether they are treated with thalidomide or other immunosuppressive drug, and that fatigue and overeating are the most common complaints.

IT 50-35-1, Thalidomide

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(thalidomide in chronic graft-vs.-host disease after stem cell transplantation: effects on quality of life)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L128 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:850945 CAPLUS  
DOCUMENT NUMBER: 135:366733  
TITLE: Compositions and methods for the treatment of cancer  
INVENTOR(S): Zeldis, Jerome B.; Zeitlin, Andrew; Barer, Sol  
PATENT ASSIGNEE(S): Celgene Corp., USA  
SOURCE: PCT Int. Appl., 44 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087307	A2	20011122	WO 2001-US15327	20010510
WO 2001087307	A3	20020725		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
BR 2001010877	A	20030311	BR 2001-10877	20010510
EP 1307197	A2	20030507	EP 2001-935373	20010510
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2003533484	T2	20031111	JP 2001-583775	20010510
US 2002035090	A1	20020321	US 2001-853617	20010514
PRIORITY APPLN. INFO.:			US 2000-204143P P	20000515
			WO 2001-US15327 W	20010510

ED Entered STN: 23 Nov 2001

AB This invention relates to compns. comprising thalidomide and another anti-cancer drug which can be used in the treatment or prevention of cancer. Preferred anti-cancer drugs are topoisomerase inhibitors. A particular compn. comprises thalidomide, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, and irinotecan. The invention also

relates to methods of treating or preventing cancer which comprise the administration of a thalidomide and another anti-cancer drug to a patient in need of such treatment or prevention. The invention further relates to methods of reducing or avoiding adverse side effects assocd. with the administration of chemotherapy or radiation therapy which comprise the administration of thalidomide to a patient in need of such redn. or avoidance.

IT 50-35-1, Thalidomide 50-35-1D, Thalidomide, prodrug

derivs. and clathrate

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(compns. comprising thalidomide and irinotecan for treatment of cancer)

L128 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:850944 CAPLUS

DOCUMENT NUMBER: 135:366732

TITLE: Compositions and methods for the treatment of colorectal cancer

INVENTOR(S): Govindarajan, Rangaswamy; Zeitlin, Andrew

PATENT ASSIGNEE(S): Celgene Corp., USA; Board of Trustees of the University of Arkansas

SOURCE: PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087306	A2	20011122	WO 2001-US15326	20010510
WO 2001087306	C1	20021003		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1286671	A2	20030305	EP 2001-935372	20010510
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2003533483	T2	20031111	JP 2001-583774	20010510
US 2002035091	A1	20020321	US 2001-853619	20010514
PRIORITY APPLN. INFO.:			US 2000-204142P P	20000515
			WO 2001-US15326 W	20010510

ED Entered STN: 23 Nov 2001

AB This invention relates to compns. comprising thalidomide and irinotecan, which can be used in the treatment or prevention of colorectal cancer. The invention also relates to methods of treating or preventing colorectal cancer which comprise the administration of thalidomide and irinotecan to a patient in need of such treatment or prevention. The invention further relates to methods of reducing or avoiding adverse side effects assocd. with the administration of irinotecan which comprise the administration of thalidomide to a patient in need of such redn. or avoidance.

IT 50-35-1, Thalidomide 50-35-1D, Thalidomide, prodrug

derivs. and clathrates

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)  
(compsn. comprising thalidomide and irinotecan for treatment of  
colorectal cancer)

L128 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:824200 CAPLUS  
DOCUMENT NUMBER: 134:537  
TITLE: Calcium-activated potassium channel-modulating agents  
for therapeutic use  
INVENTOR(S): Jensen, Bo Skaaning; Teuber, Lene; Strobaek, Dorte;  
Christophersen, Palle; Olesen, Soren Peter  
PATENT ASSIGNEE(S): Neurosearch A/S, Den.  
SOURCE: PCT Int. Appl., 45 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069794	A2	20001123	WO 2000-DK256	20000512
WO 2000069794	A3	20020110		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2000045376	A5	20001205	AU 2000-45376	20000512
EP 1187610	A2	20020320	EP 2000-926722	20000512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002065266	A1	20020530	US 2001-984061	20011025
US 6525043	B2	20030225		
PRIORITY APPLN. INFO.:			DK 1999-656	A 19990512
			WO 2000-DK256	W 20000512

OTHER SOURCE(S): MARPAT 134:537

ED Entered STN: 24 Nov 2000

AB The invention discloses the use of a particular class of chem. compds. as  
modulators of SKCa, IKCa and BKCa calcium-activated potassium channels, as  
well as pharmaceutical compns. comprising the SK/IK/BK channel-modulating  
agents.

IT 50-35-1, Thalidomide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
(Uses)

(calcium-activated potassium channel-modulating agents for therapeutic  
use)

L128 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:604486 CAPLUS  
DOCUMENT NUMBER: 134:141424  
TITLE: Effect of thalidomide on gastrointestinal toxic  
effects of irinotecan  
AUTHOR(S): Govindarajan, R.; Heaton, K. M.; Broadwater, R.;  
Zeitlin, A.; Lang, N. P.; Hauer-Jensen, M.  
CORPORATE SOURCE: University of Arkansas for Medical Sciences, Little  
Rock, AR, 72205, USA

SOURCE: Lancet (2000), 356(9229), 566-567  
 CODEN: LANCAO; ISSN: 0140-6736  
 PUBLISHER: Lancet Ltd.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 ED Entered STN: 30 Aug 2000  
 AB Irinotecan is the only accepted second-line treatment for colorectal cancer in the USA. Doses are, however, frequently limited by assocd. late-onset diarrhea. Thalidomide has antiangiogenic and immunomodulatory properties and is being investigated as an antineoplastic. We did a pilot study of combination therapy with thalidomide and irinotecan for metastatic colorectal cancer. In an interim anal. of 9 patients, thalidomide had almost eliminated the dose-limiting gastrointestinal toxic effects of irinotecan, esp. diarrhea and nausea (each  $p < 0.0001$ ), and 8 of 9 patients were able to complete the chemotherapy course.  
 IT 50-35-1, Thalidomide  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (effect of thalidomide on gastrointestinal toxic effects of irinotecan)  
 REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L128 ANSWER 20 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:996589 CAPLUS  
 DOCUMENT NUMBER: 124:45676  
 TITLE: Immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods  
 INVENTOR(S): Mak, Vivien H. W.  
 PATENT ASSIGNEE(S): De Novo Corp, USA  
 SOURCE: PCT Int. Appl., 129 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9527510	A1	19951019	WO 1995-US4677	19950411
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9523857	A1	19951030	AU 1995-23857	19950411
EP 757558	A1	19970212	EP 1995-917009	19950411
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10500669	T2	19980120	JP 1995-526541	19950411
EP 937460	A2	19990825	EP 1999-201333	19950411
EP 937460	A3	20000405		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
US 5962477	A	19991005	US 1998-97441	19980615
US 6190691	B1	20010220	US 1998-97440	19980615
PRIORITY APPLN. INFO.:				
			US 1994-225991	A2 19940412
			US 1994-271287	A 19940706
			US 1995-400234	A 19950303
			EP 1995-917009	A3 19950411
			WO 1995-US4677	W 19950411

US 1995-463819 B1 19950605

ED Entered STN: 22 Dec 1995

AB Screening methods are provided for evaluating compds. capable of suppressing cytokine prodn. either in vitro or in vivo. The methods generally involve stimulating the prodn. of a cytokine in a cell, exposing a portion of the cells to a putative cytokine-modulating agent, and detg. subsequent levels of cytokine prodn. in the cells. Addnl., the present invention provides certain compds. identified by this method, as well as methods for treating conditions modulated by TNF. The methodol. of the invention may be used for e.g. prevention or redn. of transdermal drug delivery system-induced irritation and treatment of skin or systemic inflammatory conditions. Examples include e.g. inhibition of stimulated cytokine prodn. in human cells by a variety of drugs. Verapamil was effective in preventing the development of skin inflammatory responses in mice.

IT 50-35-1, Thalidomide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

L128 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:756439 CAPLUS

DOCUMENT NUMBER: 123:132879

TITLE: Method of treating intestinal disorders with anti-TNF agents

INVENTOR(S): Jackson, Graham Douglas Fischer

PATENT ASSIGNEE(S): Unisearch Ltd., Australia

SOURCE: PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9515179	A1	19950608	WO 1994-AU745	19941201
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2177570	AA	19950608	CA 1994-2177570	19941201
AU 9511879	A1	19950619	AU 1995-11879	19941201
EP 732938	A1	19960925	EP 1995-902712	19941201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09505812	T2	19970610	JP 1994-515299	19941201
PRIORITY APPLN. INFO.:			AU 1993-2740	19931201
			AU 1994-8325	19940921
			WO 1994-AU745	19941201

ED Entered STN: 25 Aug 1995

AB The present invention provides a method of treating or preventing an intestinal disorder caused by an elevated level of TNF in the lumen of the intestine. The method involves administering to the subject an agent which reduces the action of the intraluminal TNF or reduces the prodn. or accumulation of intraluminal TNF. The agent may be any of a no. of known anti-TNF agents, however, it is preferred that the agent is an anti-TNF antibody. It is also preferred that the agent is administered directly



into the intestine.

IT 50-35-1, Thalidomide

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(anti-TNF agents for treating intestinal disorders)

L128 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1962:445825 CAPLUS

DOCUMENT NUMBER: 57:45825

ORIGINAL REFERENCE NO.: 57:9143h-i,9144a-b

TITLE: Pharmacologic study of lipoxidase

AUTHOR(S): Muset, Pedro Puig

SOURCE: Therapie (1960), 15, 199-216

CODEN: THERAP; ISSN: 0040-5957

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

ED Entered STN: 22 Apr 2001

AB Lipoxidase (I) was prepd. from soybeans with an activity of 21,000 units/mg. I was inhibited by N-phthaloylglutamimide, lysergic diethylamide, chlorpromazine, morphine, azacyclonol, and serotonin from 70 to 20% and was potentiated by meprobamate, cocaine, Na glutamate, diethylbarbituric acid, glutamine, dextromoramide, aminobutyric acid, and iproniazid. The I-linoleic acid system oxidized promethazine and pptd. cystine as cystine. The L.D.50 of I in mice was 500, 400, and 80 mg./kg., resp., for subcutaneous, intraperitoneal, and intravenous applications. In female rats the intraperitoneal L.D.50 was 100-150 mg./kg. I provoked in rats a temporary excitement followed by a long-lasting somnolence and dyspnea. High I doses paralyzed the posterior legs and produced diarrhea and loss of wt. In mice, guinea pigs, anti dogs I had similar effects. Necropsic examn. showed pleural exudates. Pulmonary histol. showed severe intraalveolar exudation; after chronic oral I results were like bronchitis. I given ad libitum to mice in their drinking water (1 mg./ml.) for 40 days produced a poor condition and alopecia of the head and back; hair follicles in these regions were atrophied. Upon topical or intradermal application of I and linoleic acid, an alopecia developed, which was reversible at 1st but was followed by necrotic ulcerations. In guinea pigs, 250 mg. I given subcutaneously increased urinary creatinine elimination up to 35 mg./day; catalase (II) (870 units) had the same effect. Uric acid elimination increased to 0.4 mg./day, and 150 mg. I increased urinary 17-hydroxy corticosteroid output by 2- to 10-fold; II alone or after I administration inhibited this effect. The survival time of mice in hypoxia increased by 28% after injecting 500 mg. I/kg. On applying I and a grease the increase was of 61-73%. II increased the survival time by 120% and I plus II by 200%. 30 references.

IT 50-35-1, Phthalimide, N-(2,6-dioxo-3-piperidyl)-  
(lipoxidase activity response to)

L128 ANSWER 23 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2002457968 EMBASE

TITLE: Evaluation of chronic diarrhea in patients with human immunodeficiency virus infection.

AUTHOR: Oldfield III E.C.

CORPORATE SOURCE: Dr. E.C. Oldfield III, Division of Infectious Diseases,  
Department of Medicine, Eastern Virginia Medical School,  
Norfolk, VA, United States

SOURCE: Reviews in Gastroenterological Disorders, (2002) 2/4  
(176-188).

Refs: 76

ISSN: 1533-001X CODEN: RGDEAK

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology

006 Internal Medicine  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Chronic diarrhea is a common problem for patients with human immunodeficiency virus infection, especially those with advanced disease. The extent of evaluation and whether to do flexible sigmoidoscopy, colonoscopy, and/or upper endoscopy have been areas of significant debate. Based upon the marked improvement in long-term survival since the introduction of highly active antiretroviral therapy, a comprehensive evaluation is currently justified. A stepwise approach to the evaluation of chronic diarrhea appears to be the best approach. The first step is a history, with a focus on any association between the onset of diarrhea and the institution of protease inhibitor therapy, which is associated with significant diarrhea in many patients. If there is no temporal association with antiretroviral therapy, the next step is examination of stool for bacterial and protozoal pathogens. If the stool studies are negative, the next step is to proceed to colonoscopy. Flexible sigmoidoscopy alone has been noted to miss up to 39% of cases of cytomegalovirus colitis. The inclusion of ileoscopy and biopsy of the terminal ileum during colonoscopy has a significant yield for microsporidiosis, which may obviate the need for upper endoscopy. The highest yield can be expected in patients with fever, weight loss, and a CD4 count of under 200 cells/mm<sup>3</sup>, especially those with a CD4 count less than 50 cells/mm<sup>3</sup>. .COPYRG. 2002 MedReviews, LLC.

L128 ANSWER 24 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 1998109788 EMBASE

TITLE: [Infectious diarrhea].  
 DIARRHEES INFECTIEUSES.

AUTHOR: Delarive J.; Guyot J.

CORPORATE SOURCE: Dr. J. Delarive, Division de Gastro-Enterologie, CHUV, 1011  
 Lausanne, Switzerland

SOURCE: Medecine et Hygiene, (28 Jan 1998) 56/2194 (223-226).  
 Refs: 63

ISSN: 0025-6749 CODEN: MEHGAB

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology  
 037 Drug Literature Index  
 048 Gastroenterology

LANGUAGE: French

SUMMARY LANGUAGE: English; French

AB Utility of prophylactic antibiotherapy has been confirmed in traveller's diarrhea. However it should be prescribed only to certain categories of travellers (underlying illness, type and destination of the trip). Quinolones are the best treatment for traveller's diarrhea, because of the emergence of resistance to co-trimoxazole. The efficacy of Socrhomycin bouldardil has been confirmed in the prevention of antibiotic associated diarrhea. In AIDS patients, diarrhea due to cryptosporidium responds partially to paromomycin. Albendazole improves diarrhea due to microsporidium in AIDS. Thalidomide should be tried in patients non-responding to albendazole. Co-trimaxazole is efficient in diarrhea due to cyclospora species and a long term treatment prevents relapse in HIV patients. Octreotide may be useful in selected patients with refractory diarrhea.

L128 ANSWER 25 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN

ACCESSION NUMBER: 1998208850 EMBASE  
 TITLE: Diarrhea and HIV infection.  
 AUTHOR: Bellosillo N.A.; Gorbach S.L.  
 CORPORATE SOURCE: Dr. N.A. Bellosillo, Geographic Med./Infect. Dis. Div., New England Medical Center, 750 Washington Street, Boston, MA 02111, United States. nbelloso@opal.tufts.edu  
 SOURCE: Infectious Diseases in Clinical Practice, (1998) 7/5 (213-219).  
 Refs: 35  
 ISSN: 1056-9103 CODEN: IDCPEY  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal; (Short Survey)  
 FILE SEGMENT: 004 Microbiology  
 006 Internal Medicine  
 037 Drug Literature Index  
 048 Gastroenterology  
 LANGUAGE: English

L128 ANSWER 26 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN

ACCESSION NUMBER: 97057562 EMBASE  
 DOCUMENT NUMBER: 1997057562  
 TITLE: [Infectious diarrhea].  
 DIARRHEES INFECTIEUSES.  
 AUTHOR: Delarive J.; Jornod P.; Guyot J.  
 CORPORATE SOURCE: Dr. J. Delarive, Division de Gastro-Enterologie, Departement de Medecine Interne, CHUV, 1011 Lausanne, Switzerland  
 SOURCE: Medecine et Hygiene, (1997) 55/2148 (188-191).  
 Refs: 63  
 ISSN: 0025-6749 CODEN: MEHGAB  
 COUNTRY: Switzerland  
 DOCUMENT TYPE: Journal; (Short Survey)  
 FILE SEGMENT: 004 Microbiology  
 048 Gastroenterology  
 037 Drug Literature Index  
 LANGUAGE: French  
 SUMMARY LANGUAGE: English; French

AB Utility of prophylactic antibiotherapy has been confirmed in traveller's diarrhea. However, it should be prescribed only to certain categories of travellers (underlying illness, type and destination of the trip). Quinolones are the best treatment of traveller's diarrhea, because of the emergence of resistances to co-trimoxazole. The efficacy of *Saccharomyces boulardii* has been confirmed in the prevention of antibiotics associated diarrhea. In AIDS patients, diarrhea due to *cryptosporidium* responds partially to paromomycin. Albendazole improves diarrhea due to *microsporidium* in AIDS. Cotrimoxazole is efficient in diarrhea due to *cyclospora* species and a long term treatment prevents relapse in HIV patients. Octreotide may be useful in selected patients with refractory diarrhea.

L128 ANSWER 27 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN

ACCESSION NUMBER: 96162637 EMBASE  
 DOCUMENT NUMBER: 1996162637  
 TITLE: [Loss of body weight increases the risk of disease progression in HIV infected patients. Therapy of diarrhea].  
 VERLUST VON KÖRPERZELLMASSE ERHOHT DAS PROGRESSIONSRISIKO BEI HIV. WEITERESSEN - SO LANGE WIE MOGLICH!  
 AUTHOR: Bierl H.  
 SOURCE: Therapiewoche, (1996) 46/17 (929-930).

ISSN: 0040-5973 CODEN: THEWA6  
COUNTRY: Germany  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 004 Microbiology  
005 General Pathology and Pathological Anatomy  
026 Immunology, Serology and Transplantation  
048 Gastroenterology  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: German  
SUMMARY LANGUAGE: German

L128 ANSWER 28 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 96280928 EMBASE  
DOCUMENT NUMBER: 1996280928  
TITLE: Thalidomide trial for diarrhea.  
SOURCE: AIDS Patient Care and STDs, (1996) 10/4 (263).  
ISSN: 0893-5068 CODEN: APCSF6  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Note  
FILE SEGMENT: 006 Internal Medicine  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English

L128 ANSWER 29 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 95172812 EMBASE  
DOCUMENT NUMBER: 1995172812  
TITLE: The treatment of microsporidial diarrhoea with thalidomide [7].  
AUTHOR: Sharpstone D.; Rowbottom A.; Nelson M.; Gazzard B.  
CORPORATE SOURCE: Department of HIV-GUM, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9TH, United Kingdom  
SOURCE: AIDS, (1995) 9/6 (658-659).  
ISSN: 0269-9370 CODEN: AIDSET  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Letter  
FILE SEGMENT: 004 Microbiology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English

L128 ANSWER 30 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 93257227 EMBASE  
DOCUMENT NUMBER: 1993257227  
TITLE: [Usefulness of talidomide therapy in the management of chronic diarrhea in patients with AIDS].  
TALIDOMIDA EN LA DIARREA CRONICA DEL ENFERMO CON SIDA.  
COMUNICACION PRELIMINAR A PROPOSITO DE UN CASO.  
AUTHOR: Martino O.; Peña M.C.; Brusca S.; Cascardo S.; Murphy A.; Orduna T.  
CORPORATE SOURCE: Centro Municipal de Patologia Reg., Argentina y Medicina Tropical, Hospital de Infecciosas 'F.J. Muniz', Uspallata 2272,1282 Buenos Aires, Argentina  
SOURCE: Prensa Medica Argentina, (1993) 80/2 (71-73).  
ISSN: 0032-745X CODEN: PMARAU  
COUNTRY: Argentina

DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 004 Microbiology  
048 Gastroenterology  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: Spanish  
SUMMARY LANGUAGE: Spanish; English

=> fil medl

FILE 'MEDLINE' ENTERED AT 13:16:48 ON 20 JUL 2004

FILE LAST UPDATED: 17 JUL 2004 (20040717/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que l48 nos; d que nos l51; s l48 or l51; fil embase; d que nos l78;d que nos l80 ;d que nos l89; d que nos l90

L2 STR  
L4 10 SEA FILE=REGISTRY FAM FUL L2  
L13 2298 SEA FILE=MEDLINE ABB=ON L4 OR IRINOTECAN OR CPT 11 OR CPT11  
OR SN 38 11 OR SN3811 OR CAMPTOTHECIN 11 OR CAMPTOSAR#  
L16 2320 SEA FILE=MEDLINE ABB=ON CAMPTOTHECIN/CT(L)AA/CT  
L37 2628 SEA FILE=MEDLINE ABB=ON THALIDOMIDE/CT  
L48 7 SEA FILE=MEDLINE ABB=ON L13 AND L16 AND L37

L37 2628 SEA FILE=MEDLINE ABB=ON THALIDOMIDE/CT  
L46 42202 SEA FILE=MEDLINE ABB=ON DRUG SYNERGISM/CT  
L49 19 SEA FILE=MEDLINE ABB=ON L37/MAJ AND L46  
L50 1512973 SEA FILE=MEDLINE ABB=ON C4./CT = *Neoplasms*  
L51 10 SEA FILE=MEDLINE ABB=ON L49 AND L50

L129 17 L48 OR L51

FILE 'EMBASE' ENTERED AT 13:17:13 ON 20 JUL 2004  
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE COVERS 1974 TO 15 Jul 2004 (20040715/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L67 5431 SEA FILE=EMBASE ABB=ON THALIDOMIDE/CT OR THALIDOMIDE DERIVATIV  
E/CT  
L75 4244 SEA FILE=EMBASE ABB=ON IRINOTECAN/CT  
L76 30372 SEA FILE=EMBASE ABB=ON DRUG POTENTIATION/CT  
L78 6 SEA FILE=EMBASE ABB=ON L67(L)CB/CT AND L75(L)CB/CT AND L76

*CB = drug combination*

L67 5431 SEA FILE=EMBASE ABB=ON THALIDOMIDE/CT OR THALIDOMIDE DERIVATIV  
E/CT  
L76 30372 SEA FILE=EMBASE ABB=ON DRUG POTENTIATION/CT

L79 29609 SEA FILE=EMBASE ABB=ON CANCER COMBINATION CHEMOTHERAPY/CT  
 L80 6 SEA FILE=EMBASE ABB=ON L67 (L) CB/CT AND L79 AND L76

L67 5431 SEA FILE=EMBASE ABB=ON THALIDOMIDE/CT OR THALIDOMIDE DERIVATIV  
 E/CT  
 L76 30372 SEA FILE=EMBASE ABB=ON DRUG POTENTIATION/CT  
 L82 549909 SEA FILE=EMBASE ABB=ON ANTINEOPLASTIC AGENT+NT/CT  
 L83 37 SEA FILE=EMBASE ABB=ON L82 (L) CB/CT AND L67 (L) CB/CT AND L76  
 L88 10211 SEA FILE=EMBASE ABB=ON L76/MAJ  
 L89 1 SEA FILE=EMBASE ABB=ON L88 AND L83

L67 5431 SEA FILE=EMBASE ABB=ON THALIDOMIDE/CT OR THALIDOMIDE DERIVATIV  
 E/CT  
 L76 30372 SEA FILE=EMBASE ABB=ON DRUG POTENTIATION/CT  
 L82 549909 SEA FILE=EMBASE ABB=ON ANTINEOPLASTIC AGENT+NT/CT  
 L85 549 SEA FILE=EMBASE ABB=ON L67 (L) CB/CT  
 L86 243 SEA FILE=EMBASE ABB=ON L85/MAJ  
 L87 16 SEA FILE=EMBASE ABB=ON L86 AND L82 (L) CB/CT AND L76  
 L90 4 SEA FILE=EMBASE ABB=ON L87 AND GENERAL REVIEW/DT

=> s 178 or 180 or 189 or 190; fil capl; d que nos 1110; d que nos 1114; s 1110 or 1114  
 L130 13 L78 OR L80 OR L89 OR L90

FILE 'CAPLUS' ENTERED AT 13:17:30 ON 20 JUL 2004  
 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
 PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
 COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 20 Jul 2004 VOL 141 ISS 4  
 FILE LAST UPDATED: 19 Jul 2004 (20040719/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L2 STR  
 L4 10 SEA FILE=REGISTRY FAM FUL L2  
 L6 STR  
 L8 66 SEA FILE=REGISTRY FAM FUL L6  
 L103 1473 SEA FILE=CAPLUS ABB=ON L4  
 L104 1669 SEA FILE=CAPLUS ABB=ON L8  
 L109 61712 SEA FILE=CAPLUS ABB=ON POTENTIAT?/OBI OR SYNERG?/OBI  
 L110 2 SEA FILE=CAPLUS ABB=ON L103 AND L104 AND L109

L6 STR  
 L8 66 SEA FILE=REGISTRY FAM FUL L6  
 L111 178381 SEA FILE=CAPLUS ABB=ON ANTITUMOR AGENTS+OLD/CT  
 L114 3 SEA FILE=CAPLUS ABB=ON L8 AND L111 AND POTENTIAT?/OBI

L131 4 L110 OR L114

=> dup rem l129,l131,l130  
 FILE 'MEDLINE' ENTERED AT 13:17:38 ON 20 JUL 2004

FILE 'CAPLUS' ENTERED AT 13:17:38 ON 20 JUL 2004  
 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
 PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
 COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 13:17:38 ON 20 JUL 2004  
 COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.  
 PROCESSING COMPLETED FOR L129  
 PROCESSING COMPLETED FOR L131  
 PROCESSING COMPLETED FOR L130  
 L132 33 DUP REM L129 L131 L130 (1 DUPLICATE REMOVED)  
 ANSWERS '1-17' FROM FILE MEDLINE  
 ANSWERS '18-21' FROM FILE CAPLUS  
 ANSWERS '22-33' FROM FILE EMBASE

=> d ibib ed ab hitrn 1-33; fil hom

L132 ANSWER 1 OF 33 MEDLINE on STN  
 ACCESSION NUMBER: 2004217209 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 15114711  
 TITLE: Report of two cases with pleural effusion and ascites that  
 responded dramatically to the combination of thalidomide,  
 celecoxib, irinotecan, and CDDP infused in  
 thoracic and abdominal cavities.  
 AUTHOR: Hada Masato  
 CORPORATE SOURCE: Surgical Dept. Ashitaka Hospital.  
 SOURCE: Gan to kagaku ryoho. Cancer & chemotherapy, (2004 Apr) 31  
 (4) 613-7.  
 Journal code: 7810034. ISSN: 0385-0684.  
 PUB. COUNTRY: Japan  
 DOCUMENT TYPE: (CASE REPORTS)  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: Japanese  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200405  
 ENTRY DATE: Entered STN: 20040430  
 Last Updated on STN: 20040520  
 Entered Medline: 20040519

ED Entered STN: 20040430  
 Last Updated on STN: 20040520  
 Entered Medline: 20040519

AB Malignant pleural effusion (PE) and ascites are associated with highly  
 symptomatic, advanced-stage cancers. These fluid accumulations cause  
 severe symptoms such as abdominal distention, shortness of breath,  
 cachexia, anorexia, and fatigue. Malignant PE and ascites have  
 consistently been shown to indicate a poor prognosis in advanced-stage  
 cancer patients, being associated with high morbidity and mortality. The



efficacy of this treatment is variable and does not prolong the survival of cancer patients. Clearly, a more effective therapy for malignant PE and ascites is needed. Vascular permeability factor (VPF) from malignant ascites and PE have been hypothesized to be responsible for the fluid accumulations. In addition, malignant PE and ascites contain high levels of biologically active VEGF. VEGF was discovered as a potent angiogenesis stimulator and recognized to be VPF. Increased amounts of COX-2 have been detected in epithelial and stromal cells and COX-2 in mammary tissue is sufficient to induce cancer. It is suggested that COX-2 stimulates angiogenesis. A combination of molecular target inhibitors (thalidomide and celecoxib) and standard cytotoxic drugs appear to increase efficacy of each drug, decrease the side effects of cytotoxic drugs and prolong life.

L132 ANSWER 2 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2004006963 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 14704038  
TITLE: The bisphosphonate zoledronic acid induces cytotoxicity in human myeloma cell lines with enhancing effects of dexamethasone and thalidomide.  
AUTHOR: Ural A Ugur; Yilmaz M Ilker; Avcu Ferit; Pekel Aysel; Zerman Murat; Nevruz Oral; Sengul Ali; Yalcin Atilla  
CORPORATE SOURCE: Department of Hematology, Gulhane Military Medical Academy, School of Medicine, Ankara, Turkey.. aural@gata.edu.tr  
SOURCE: International journal of hematology, (2003 Dec) 78 (5) 443-9.  
Journal code: 9111627. ISSN: 0925-5710.  
PUB. COUNTRY: Ireland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200404  
ENTRY DATE: Entered STN: 20040106  
Last Updated on STN: 20040428  
Entered Medline: 20040427  
ED Entered STN: 20040106  
Last Updated on STN: 20040428  
Entered Medline: 20040427  
AB Bisphosphonates have recently been introduced in the therapeutic armamentarium for long-term treatment of patients with multiple myeloma. These pyrophosphate analogs not only reduce the occurrence of skeletal events but also provide clinical benefit to patients and improve the survival of some of them. The existence of these capabilities raises the possibility that these compounds may have a direct antiproliferative effect on tumor cells. To investigate whether these drugs exert a direct antitumor effect, we exposed human myeloma cell lines ARH-77 and RPMI-8226 to increasing concentrations of zoledronic acid (ZOL) in vitro. A concentration- but not time-dependent cytotoxic effect was detected with drug treatment of ARH-77 and RPMI-8226 cell lines (30% and 60% at 48 hours and 38% and 62% at 72 hours, respectively, for 50 microm of ZOL). Cytotoxicity was not due to ZOL-induced chelation of extracellular calcium as shown by control experiments with the calcium chelator ethylene glycol-bis(beta-aminoethylether)-N,N,N',N'-tetraacetic acid. Addition of the competitive inhibitor of the nitric oxide synthase N omega-nitro-L-arginine methyl ester did not modulate ZOL-induced cytotoxicity. However, a decrease in the number of apoptotic cells was detected when protein kinase C was inhibited by addition of staurosporine to ZOL-containing cultures. Cytotoxicity also was increased by addition of dexamethasone (Dex) and thalidomide (Thal) to ARH-77 and RPMI-8226 cultures. We demonstrated that exposing myeloma cell lines ARH-77 and RPMI-8226 to ZOL inhibits cell growth in a dose-dependent but not a time-dependent manner and that combination of Dex and Thal with ZOL induces apoptotic cell death, providing a rationale for potential

applications in vivo.

L132 ANSWER 3 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2003412871 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12952300  
TITLE: Current chemotherapy for glioblastoma.  
AUTHOR: Parney Ian F; Chang Susan M  
CORPORATE SOURCE: Neuro-Oncology Service, Department of Neurological Surgery,  
University of California San Francisco, San Francisco,  
California 94143-0350, USA.  
SOURCE: Cancer journal (Sudbury, Mass.), (2003 May-Jun) 9 (3)  
149-56. Ref: 81  
Journal code: 100931981. ISSN: 1528-9117.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200312  
ENTRY DATE: Entered STN: 20030904  
Last Updated on STN: 20031218  
Entered Medline: 20031204

ED Entered STN: 20030904  
Last Updated on STN: 20031218  
Entered Medline: 20031204

AB INTRODUCTION: Glioblastoma multiforme continues to be associated with a  
dismal prognosis, despite aggressive therapy. What limited therapeutic  
impact that has been made has come via multimodality treatment in which  
chemotherapy plays an important role. In this manuscript, we review  
current chemotherapy options for glioblastomas. METHODS: The current  
literature concerning glioblastoma multiforme chemotherapy was reviewed.  
In addition to a review of landmark references, a MEDLINE search of the  
literature published from January 2000 to November 2002 was performed  
using the key words "chemotherapy AND malignant glioma" and limiting  
responses to clinical trials. RESULTS: Several cytotoxic chemotherapeutic  
agents that are efficacious in treating glioblastoma are in common  
clinical use. These can be classified as first-line or second-line  
agents, depending on their efficacy. In addition, cytostatic chemotherapy  
agents are beginning to play a role in glioblastoma treatment. Finally,  
new methods to deliver high chemotherapy doses to brain tumors hold  
promise for future therapies. CONCLUSIONS: Despite the overall poor  
prognosis of patients with glioblastoma multiforme, multimodality  
treatment and chemotherapy in particular improve outcome, and  
chemotherapeutic options are beginning to have an increased impact.  
Strategies currently in clinical trials may improve this impact more in  
the future.

L132 ANSWER 4 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2003561678 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 14649541  
TITLE: Effect of 3-fluorothalidomide and 3-methylthalidomide  
enantiomers on tumor necrosis factor production and  
antitumor responses to the antivascular agent  
5,6-dimethylxanthenone-4-acetic acid (DMXAA).  
AUTHOR: Chung Francisco; Palmer Brian D; Muller George W; Man  
Hon-Wah; Kestell Phillip; Baguley Bruce C; Ching Lai-Ming  
CORPORATE SOURCE: Auckland Cancer Society Research Center, Faculty of Medical  
and Health Sciences, The University of Auckland, Auckland,  
New Zealand.  
SOURCE: Oncology research, (2003) 14 (2) 75-82.  
Journal code: 9208097. ISSN: 0965-0407.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200407  
ENTRY DATE: Entered STN: 20031216  
Last Updated on STN: 20040703  
Entered Medline: 20040702

ED Entered STN: 20031216  
Last Updated on STN: 20040703  
Entered Medline: 20040702

AB 5,6-Dimethylxanthenone-4-acetic acid (DMXAA) is an antivasular drug that induces tumor necrosis factor (TNF) in mice. Thalidomide inhibits TNF induction by DMXAA and also potentiates its antitumor activity. We investigated whether these effects were enantiomer specific, using the R- or S-enantiomers of two nonracemizable thalidomide analogues. Racemic 3-fluorothalidomide (3FThal) and racemic 3-methylthalidomide (3MeThal) were separated into enantiomers of greater than 98% optical purity using preparative chiral column chromatography. C57Bl/6 mice implanted with subcutaneous Colon 38 tumors were treated with DMXAA (25 mg/kg) alone or together with the pure R- or S-enantiomers by a single i.p. injection. TNF levels in the serum or tumor tissues 3 h after treatment were measured using ELISAs and tumor growth was also measured. 3FThal and 3MeThal, at their respective single maximum tolerated doses (MTD) of 15 and 50 mg/kg, were more toxic in mice than thalidomide (100 mg/kg). The R- and S-enantiomers of either 3FThal or 3MeThal, at their respective MTD, inhibited DMXAA-induced TNF activity in serum and tumor tissue, but no significant differences were observed between the enantiomers. Coadministration of racemic or enantiomers of 3FThal or 3MeThal at their respective MTD did not potentiate the antitumor responses above that obtained with DMXAA alone, and no enantioselectivity was apparent. We conclude that there is no advantage in using the nonracemizable thalidomide analogues to improve the antitumor activity of DMXAA.

L132 ANSWER 5 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2003125975 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12639293  
TITLE: IFN-alpha2b and thalidomide synergistically inhibit tumor-induced angiogenesis.  
AUTHOR: Bauer Joseph A; Morrison Bei H; Grane Ronald W; Jacobs Barbara S; Borden Ernest C; Lindner Daniel J  
CORPORATE SOURCE: Taussig Cancer Center, The Cleveland Clinic Foundation, Cleveland, OH 44195, USA.  
SOURCE: Journal of interferon & cytokine research : official journal of the International Society for Interferon and Cytokine Research, (2003 Jan) 23 (1) 3-10.  
Journal code: 9507088. ISSN: 1079-9907.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200309  
ENTRY DATE: Entered STN: 20030318  
Last Updated on STN: 20030928  
Entered Medline: 20030926

ED Entered STN: 20030318  
Last Updated on STN: 20030928  
Entered Medline: 20030926

AB Angiogenesis is an absolute requirement for tumor growth and metastasis. The purpose of this study was to evaluate the antiangiogenic activity of interferon-alpha2b (IFN-alpha2b) and thalidomide, as single agents and in combination. The murine dermis model was used to assess tumor-induced

angiogenesis in nude mice. Human ACHN (renal), NIH-OVCA-3 (ovarian), LNCaP (prostate), and SK-Mel-1 (melanoma) tumor cells were inoculated intradermally into the flanks of nude mice. IFN-alpha2b and thalidomide, administered daily, were effective inhibitors of angiogenesis induced by all four tumor types. The combination of IFN-alpha2b and thalidomide caused a synergistic decrease in mean vessel count in tumors that were resistant to the antiproliferative effects of IFN-alpha2b and thalidomide in vitro. This enhanced suppression of angiogenesis translated into synergistic antitumor activity in a xenograft model. Pegylated IFN-alpha (PEG-IFN-alpha2b) (10(6) U) administered once in 10 days was as effective as daily IFN-alpha2b treatment (10(6) U x 10 days). IFN-alpha2b and thalidomide have potentiated antiangiogenic activity when used in combination. A single dose of PEG-IFN-alpha2b (10(6) U) was as effective at suppressing vessel growth as an equivalent dose of IFN-alpha2b given daily for 10 days.

L132 ANSWER 6 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2002298600 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12040298  
TITLE: Thalidomide and irinotecan-associated diarrhea.  
AUTHOR: Tchekmedyian N Simon  
SOURCE: American journal of clinical oncology : official  
publication of the American Radium Society, (2002 Jun) 25  
(3) 324.  
Journal code: 8207754. ISSN: 0277-3732.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (CASE REPORTS)  
Letter  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200206  
ENTRY DATE: Entered STN: 20020602  
Last Updated on STN: 20020628  
Entered Medline: 20020627  
ED Entered STN: 20020602  
Last Updated on STN: 20020628  
Entered Medline: 20020627

L132 ANSWER 7 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2002296330 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12036884  
TITLE: Apoptotic signaling induced by immunomodulatory thalidomide  
analogs in human multiple myeloma cells: therapeutic  
implications.  
AUTHOR: Mitsiades Nicholas; Mitsiades Constantine S; Poulaki  
Vassiliki; Chauhan Dharminder; Richardson Paul G; Hideshima  
Teru; Munshi Nikhil C; Treon Steven P; Anderson Kenneth C  
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute,  
Harvard Medical School, Boston, MA 02115, USA.  
CONTRACT NUMBER: PO-1 78378  
SOURCE: Blood, (2002 Jun 15) 99 (12) 4525-30.  
Journal code: 7603509. ISSN: 0006-4971.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200207  
ENTRY DATE: Entered STN: 20020531  
Last Updated on STN: 20020712  
Entered Medline: 20020711  
ED Entered STN: 20020531  
Last Updated on STN: 20020712

Entered Medline: 20020711

AB Thalidomide (Thal) achieves responses even in the setting of refractory multiple myeloma (MM). Although increased angiogenesis in MM bone marrow and the antiangiogenic effect of Thal formed the empiric basis for its use in MM, we have shown that Thal and its immunomodulatory analogs (IMiDs) directly induce apoptosis or growth arrest of MM cells, alter adhesion of MM cells to bone marrow stromal cells, inhibit the production of cytokines (interleukin-6 and vascular endothelial growth factor) in bone marrow, and stimulate natural killer cell anti-MM immunity. In the present study, we demonstrate that the IMiDs trigger activation of caspase-8, enhance MM cell sensitivity to Fas-induced apoptosis, and down-regulate nuclear factor (NF)-kappa B activity as well as expression of cellular inhibitor of apoptosis protein-2 and FLICE inhibitory protein. IMiDs also block the stimulatory effect of insulinlike growth factor-1 on NF-kappa B activity and potentiate the activity of TNF-related apoptosis-inducing ligand (TRAIL/Apo2L), dexamethasone, and proteasome inhibitor (PS-341) therapy. These studies both delineate the mechanism of action of IMiDs against MM cells in vitro and form the basis for clinical trials of these agents, alone and coupled with conventional and other novel therapies, to improve outcome in MM.

L132 ANSWER 8 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2002274258 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 12014864  
TITLE: **Irinotecan**/thalidomide in metastatic colorectal cancer.  
AUTHOR: Govindarajan Rangaswamy  
CORPORATE SOURCE: University of Arkansas for Medical Sciences, Little Rock 72205, USA.. govindarajanrang@uams.edu  
SOURCE: Oncology (Williston Park, N.Y.), (2002 Apr) 16 (4 Suppl 3) 23-6. Ref: 17  
Journal code: 8712059. ISSN: 0890-9091.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200211  
ENTRY DATE: Entered STN: 20020517  
Last Updated on STN: 20021211  
Entered Medline: 20021107

ED Entered STN: 20020517  
Last Updated on STN: 20021211  
Entered Medline: 20021107

AB The prognosis for patients with metastatic colorectal cancer is poor. Use of **irinotecan** (CPT-11, **Camptosar**) results in modest response rates of approximately 20% in refractory patients diagnosed with this advanced stage of disease and offers a side-effect profile that improves on that of previous standard treatments. Thalidomide (Thalomid) has antiangiogenic properties, and angiogenesis has been shown to influence the outcome of colon cancer patients. A good response rate and acceptable tolerability regarding gastrointestinal effects were demonstrated in a pilot study of the **irinotecan** /thalidomide combination in patients with metastatic colorectal cancer. This combination is being assessed at the University of Arkansas for Medical Sciences as second-line therapy in a phase II trial. Patients with metastatic colorectal cancer are receiving 350 mg/m<sup>2</sup> of **irinotecan** every 3 weeks plus 400 mg/m<sup>2</sup>/d of thalidomide. Preliminary response and safety data are presented for 18 enrolled patients.

L132 ANSWER 9 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2001555740 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11602422  
TITLE: Thalidomide and thrombosis in patients with multiple  
myeloma.  
AUTHOR: Camba L; Peccatori J; Pescarollo A; Tresoldi M; Corradini  
P; Bregni M  
SOURCE: Haematologica, (2001 Oct) 86 (10) 1108-9.  
Journal code: 0417435. ISSN: 0390-6078.  
PUB. COUNTRY: Italy  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Letter  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200210  
ENTRY DATE: Entered STN: 20011017  
Last Updated on STN: 20021004  
Entered Medline: 20021003  
ED Entered STN: 20011017  
Last Updated on STN: 20021004  
Entered Medline: 20021003

L132 ANSWER 10 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2000414475 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 10950238  
TITLE: Effect of thalidomide on gastrointestinal toxic effects of  
**irinotecan**.  
AUTHOR: Govindarajan R; Heaton K M; Broadwater R; Zeitlin A; Lang N  
P; Hauer-Jensen M  
SOURCE: Lancet, (2000 Aug 12) 356 (9229) 566-7.  
Journal code: 2985213R. ISSN: 0140-6736.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: (CLINICAL TRIAL)  
Letter  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS  
ENTRY MONTH: 200008  
ENTRY DATE: Entered STN: 20000907  
Last Updated on STN: 20000907  
Entered Medline: 20000829  
ED Entered STN: 20000907  
Last Updated on STN: 20000907  
Entered Medline: 20000829

AB **Irinotecan** is the only accepted second-line treatment for  
colorectal cancer in the USA. Doses are, however, frequently limited by  
associated late-onset diarrhoea. Thalidomide has antiangiogenic and  
immunomodulatory properties and is being investigated as an  
antineoplastic. We did a pilot study of combination therapy with  
thalidomide and **irinotecan** for metastatic colorectal cancer. In  
an interim analysis of nine patients, thalidomide had almost eliminated  
the dose-limiting gastrointestinal toxic effects of **irinotecan**,  
especially diarrhoea and nausea (each  $p < 0.0001$ ), and eight of nine  
patients were able to complete the chemotherapy course.

L132 ANSWER 11 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 2001192568 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 11204671  
TITLE: **Irinotecan** and thalidomide in metastatic  
colorectal cancer.  
AUTHOR: Govindarajan R  
CORPORATE SOURCE: Division of Hematology/Oncology, University of Arkansas for  
Medical Sciences, Little Rock, Arkansas, USA.

SOURCE: Oncology (Williston Park, N.Y.), (2000 Dec) 14 (12 Suppl 13) 29-32.  
Journal code: 8712059. ISSN: 0890-9091.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)  
(CLINICAL TRIAL)  
(CLINICAL TRIAL, PHASE II)  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200104

ENTRY DATE: Entered STN: 20010410  
Last Updated on STN: 20010410  
Entered Medline: 20010405

ED Entered STN: 20010410  
Last Updated on STN: 20010410  
Entered Medline: 20010405

AB Fifteen patients with metastatic colorectal cancer were treated with irinotecan (CPT-11, Camptosar) at 300 to 350 mg/m<sup>2</sup> every 21 days and thalidomide (Thalomid) at 400 mg/d. Of the 15 patients, 11 were in a pilot study and 4 were in an ongoing phase II protocol. There were 12 men and 3 women, with a median age of 56 years (range: 29 to 79 years). Patients were treated with a median of three cycles (range: one to eight cycles). The four patients enrolled in the formal protocol were not evaluable for response at the time of this report. Of the 11 patients in the pilot study, 10 were evaluable for response; there were two complete responses, two partial responses, and six progressions. Investigators noted a remarkable absence of grade 3/4 gastrointestinal toxicities, and concluded that further testing of the complete response and toxicity profile of the irinotecan /thalidomide regimen was warranted.

L132 ANSWER 12 OF 33 MEDLINE on STN

ACCESSION NUMBER: 1999287394 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10360649

TITLE: Thalidomide increases both intra-tumoural tumour necrosis factor-alpha production and anti-tumour activity in response to 5,6-dimethylxanthenone-4-acetic acid.

AUTHOR: Cao Z; Joseph W R; Browne W L; Mountjoy K G; Palmer B D; Baguley B C; Ching L M

CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland School of Medicine, New Zealand.

SOURCE: British journal of cancer, (1999 May) 80 (5-6) 716-23.  
Journal code: 0370635. ISSN: 0007-0920.

PUB. COUNTRY: SCOTLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199906

ENTRY DATE: Entered STN: 19990712  
Last Updated on STN: 19990712  
Entered Medline: 19990623

ED Entered STN: 19990712  
Last Updated on STN: 19990712  
Entered Medline: 19990623

AB 5,6-Dimethylxanthenone-4-acetic acid (DMXAA), synthesized in this laboratory and currently in phase I clinical trial, is a low molecular weight inducer of tumour necrosis factor-alpha (TNF-alpha). Administration of DMXAA to mice with established transplantable tumours elicits rapid vascular collapse selectively in the tumour, followed by extensive haemorrhagic necrosis mediated primarily through the production of TNF-alpha. In this report we have investigated the synthesis of

TNF-alpha mRNA in hepatic, splenic and tumour tissue. Co-administration of thalidomide with DMXAA increased anti-tumour activity and increased intra-tumoural TNF-alpha production approximately tenfold over that obtained with DMXAA alone. Thalidomide increased splenic TNF-alpha production slightly but significantly decreased serum and hepatic levels of TNF-alpha induced with DMXAA. Lipopolysaccharide (LPS) induced 300-fold higher serum TNF-alpha than did DMXAA at the maximum tolerated dose, but induced similar amounts of TNF-alpha in spleen, liver and tumour. Splenic TNF-alpha activity induced with LPS was slightly increased with thalidomide, but serum and liver TNF-alpha levels were suppressed. Thalidomide did not increase intra-tumoural TNF-alpha production induced with LPS, in sharp contrast to that obtained with DMXAA. While thalidomide improved the anti-tumour response to DMXAA, it had no effect on the anti-tumour action of LPS that did not induce a significant growth delay or cures against the Colon 38 tumour. The increase in the anti-tumour action by thalidomide in combination with DMXAA corresponded to an increase in intra-tumoural TNF-alpha production. Co-administration of thalidomide may represent a novel approach to improving selective intra-tumoural TNF-alpha production and anti-tumour efficacy of DMXAA.

L132 ANSWER 13 OF 33 MEDLINE on STN  
 ACCESSION NUMBER: 1999259140 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10328588  
 TITLE: New chemotherapy options for the treatment of malignant gliomas.  
 AUTHOR: Burton E; Prados M  
 CORPORATE SOURCE: University of California, San Francisco, Department of Neurosurgery, USA.  
 CONTRACT NUMBER: CA09291 (NCI)  
 CA13525 (NCI)  
 SOURCE: Current opinion in oncology, (1999 May) 11 (3) 157-61.  
 Ref: 24  
 Journal code: 9007265. ISSN: 1040-8746.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals; AIDS  
 ENTRY MONTH: 199906  
 ENTRY DATE: Entered STN: 19990714  
 Last Updated on STN: 19990714  
 Entered Medline: 19990628  
 ED Entered STN: 19990714  
 Last Updated on STN: 19990714  
 Entered Medline: 19990628  
 AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.

L132 ANSWER 14 OF 33 MEDLINE on STN



ACCESSION NUMBER: 1998366839 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9703279  
TITLE: Interaction of thalidomide, phthalimide analogues of thalidomide and pentoxifylline with the anti-tumour agent 5,6-dimethylxanthenone-4-acetic acid: concomitant reduction of serum tumour necrosis factor-alpha and enhancement of anti-tumour activity.  
AUTHOR: Ching L M; Browne W L; Tchernegovski R; Gregory T; Baguley B C; Palmer B D  
CORPORATE SOURCE: Auckland Cancer Society Research Centre, University of Auckland School of Medicine, New Zealand.  
SOURCE: British journal of cancer, (1998 Aug) 78 (3) 336-43.  
Journal code: 0370635. ISSN: 0007-0920.  
PUB. COUNTRY: SCOTLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals; AIDS  
ENTRY MONTH: 199808  
ENTRY DATE: Entered STN: 19980903  
Last Updated on STN: 19980903  
Entered Medline: 19980824

ED Entered STN: 19980903  
Last Updated on STN: 19980903  
Entered Medline: 19980824

AB DMXAA (5,6-dimethylxanthenone-4-acetic acid), a novel anti-tumour agent currently undergoing clinical evaluation, appears to mediate its anti-tumour effects through immune modulation and the production of the cytokine tumour necrosis factor-alpha (TNF). Our previous studies have shown that thalidomide, a potent inhibitor of TNF biosynthesis that has numerous biological effects, including inhibition of tumour angiogenesis, unexpectedly augments the anti-tumour response in mice to DMXAA. We show here that thalidomide (100 mg kg<sup>-1</sup>) has no effect when administered with inactive doses of DMXAA, and that it must be given simultaneously with an active dose of DMXAA to have its maximum potentiating effect on the growth of the murine Colon 38 adenocarcinoma. To address the issue of whether inhibition of serum TNF production is important for potentiation of anti-tumour activity, we have tested three potent analogues of thalidomide. All three analogues, when co-administered with DMXAA to mice at doses lower than those used with thalidomide, inhibited TNF production and were effective in potentiating the anti-tumour activity of DMXAA against transplanted Colon 38 tumours. One of the analogues, N-phenethyltetrafluorophthalimide, was 1000-fold more potent than thalidomide and at a dose of 0.1 mg kg<sup>-1</sup> in combination with DMXAA (30 mg kg<sup>-1</sup>) cured 100% of mice, compared with 67% for the group treated with DMXAA alone. We also tested pentoxifylline and found it to suppress TNF production in response to DMXAA and to potentiate the anti-tumour effect of DMXAA. The results are compatible with the hypothesis that pharmacological reduction of serum TNF levels might benefit the anti-tumour effects of DMXAA and suggest new strategies for therapy using this agent.

L132 ANSWER 15 OF 33 MEDLINE on STN  
ACCESSION NUMBER: 94183211 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 8135786  
TITLE: Enhancement of phorbol ester-induced production of tumor necrosis factor alpha by thalidomide.  
AUTHOR: Nishimura K; Hashimoto Y; Iwasaki S  
CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, University of Tokyo, Japan.  
SOURCE: Biochemical and biophysical research communications, (1994 Mar 15) 199 (2) 455-60.  
Journal code: 0372516. ISSN: 0006-291X.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199404  
ENTRY DATE: Entered STN: 19940428  
Last Updated on STN: 19970203  
Entered Medline: 19940421

ED Entered STN: 19940428  
Last Updated on STN: 19970203  
Entered Medline: 19940421

AB The effect of thalidomide [racemic (DL-) form and optically pure (D- and L-) forms] on tumor necrosis factor (TNF) alpha production by human leukemia cell lines (HL-60, K562 and U937) stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA) was investigated. Though thalidomide has been regarded as a specific inhibitor of TNF-alpha production, our study indicated that all forms of thalidomide enhanced (but did not inhibit) the TPA-induced TNF-alpha production by the human leukemia cell lines investigated. The effects of thalidomide on TNF-alpha production might be cell type-specific.

L132 ANSWER 16 OF 33 MEDLINE on STN

ACCESSION NUMBER: 92034660 MEDLINE

DOCUMENT NUMBER: PubMed ID: 1933837

TITLE: The thalidomide analog, EM 12, enhances  
1,2-dimethylhydrazine-induction of rat colon  
adenocarcinomas.

AUTHOR: Gershbein L L

CORPORATE SOURCE: Biochemistry and Oncology Sections, Northwest Institute for  
Medical Research, John F. Kennedy Health Care Corporation,  
Chicago, Illinois 60645.

SOURCE: Cancer letters, (1991 Nov) 60 (2) 129-33.  
Journal code: 7600053. ISSN: 0304-3835.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199112

ENTRY DATE: Entered STN: 19920124  
Last Updated on STN: 19980206  
Entered Medline: 19911202

ED Entered STN: 19920124  
Last Updated on STN: 19980206  
Entered Medline: 19911202

AB Young male Sprague-Dawley rats in 3 groups were fed a basal diet supplemented with 0.10 wt. % each of thalidomide and its imide-analog of much higher teratogenicity, EM 12. Following an induction period of 17 days on the diets, all animals were injected subcutaneously with 1,2-dimethylhydrazine at 20 mg/kg for a total of 20 weekly doses and killed on week 18 after the 20th injection. The total number of colon adenocarcinomas and their occurrence in the proximal and distal portions for the thalidomide-treated rats were similar to those of the respective controls. However, the EM 12-fed group elicited statistically significant increases both in the total and ascending colon-based adenocarcinomas as compared with the control findings, in keeping with its greater teratogenicity and embryotoxicity. The numbers of small intestinal adenocarcinomas were equally higher in the imide-fed groups in contrast to the control frequency.

L132 ANSWER 17 OF 33 MEDLINE on STN

ACCESSION NUMBER: 70131370 MEDLINE

DOCUMENT NUMBER: PubMed ID: 5417508

TITLE: Potentiating effect of thalidomide on methylcholanthrene  
oncogenesis in mice.  
AUTHOR: Miura M; Southam C M; Wuest H  
SOURCE: Experientia, (1970 Mar 15) 26 (3) 305-6.  
Journal code: 0376547. ISSN: 0014-4754.  
PUB. COUNTRY: Switzerland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 197004  
ENTRY DATE: Entered STN: 19900101  
Last Updated on STN: 19900101  
Entered Medline: 19700420

ED Entered STN: 19900101  
Last Updated on STN: 19900101  
Entered Medline: 19700420

L132 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2002:657384 CAPLUS  
DOCUMENT NUMBER: 139:30246  
TITLE: **Potentiation** of the antitumor effect of  
cyclophosphamide in mice by thalidomide  
AUTHOR(S): Ding, Qi; Kestell, Philip; Baguley, Bruce C.; Palmer,  
Brian D.; Paxton, James W.; Muller, George; Ching,  
Lai-Ming  
CORPORATE SOURCE: Faculty of Medical and Health Sciences, Auckland  
Cancer Society Research Centre, The University of  
Auckland, Auckland, N. Z.  
SOURCE: Cancer Chemotherapy and Pharmacology (2002), 50(3),  
186-192  
CODEN: CCPHDZ; ISSN: 0344-5704  
PUBLISHER: Springer-Verlag  
DOCUMENT TYPE: Journal  
LANGUAGE: English

ED Entered STN: 30 Aug 2002

AB Thalidomide has recently shown significant promise in the treatment of  
some types of cancer, and trials in combination with conventional  
chemotherapy are being undertaken. We wished to det. whether thalidomide  
potentiated the effect of cyclophosphamide, a commonly used cytotoxic  
drug, in a murine tumor model. C57Bl/6 mice implanted with s.c. Colon 38  
tumors were treated with cyclophosphamide alone or together with  
thalidomide as a single i.p. injection and tumor growth was measured.  
Concns. of cyclophosphamide, 4-hydroxycyclophosphamide,  
4-ketocyclophosphamide and 2-dechloroethylcyclophosphamide were detd. in  
plasma, liver and tumor tissue using coupled high-performance liq.  
chromatog.-mass spectrometry at different times after treatment. Results.  
Cyclophosphamide alone (220 mg/kg) induced growth delays of 11-13 days  
with no cures, whereas cyclophosphamide together with thalidomide (100  
mg/kg) cured mice of their tumors. Thalidomide at lower doses (1-20  
mg/kg) also potentiated the antitumor effect. Coadministration of  
thalidomide (100 mg/kg) dramatically decreased the clearance of  
cyclophosphamide and its metabolites from plasma and tissue, with  
corresponding increases in the area under the concn.-time curves. The  
magnitude of the effect was dependent on the dose of thalidomide over the  
range 1-20 mg/kg with no further effect at a dose of 100  
mg/kg. Conclusions. Coadministration of thalidomide and cyclophosphamide  
gave markedly greater activity against Colon 38 tumor compared with either  
drug alone. Investigation of the reason for this effect revealed  
thalidomide to possess the novel property of dramatically decreasing the  
clearance of cyclophosphamide and its metabolites.

IT 50-35-1, Thalidomide  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)  
 (thalidomide-induced **potentiation** of cyclophosphamide  
 antitumor effect in mice)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:453016 CAPLUS

DOCUMENT NUMBER: 141:1227

TITLE: Combination cancer therapy with a glutathione  
 S-transferase (GST)-activated anticancer compound and  
 another anticancer therapy

INVENTOR(S): Xu, Hua; Brown, Gail L.; Schow, Steven R.; Keck, James  
 G.

PATENT ASSIGNEE(S): Telik, Inc., USA

SOURCE: PCT Int. Appl., 38 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045593	A2	20040603	WO 2003-US36209	20031114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, FI, GB, GD, GE, GH, GM, GR, GU, HA, HE, HI, HO, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SN, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

US 2004138140 A1 20040715 US 2003-714593 20031114

PRIORITY APPLN. INFO.: US 2002-426983P P 20021115

ED Entered STN: 04 Jun 2004

AB The invention discloses a method for combination cancer therapy in a mammal, esp. a human, by administering a therapeutically effective amt. of a GST-activated anticancer compd. and a therapeutically ED of another anticancer therapy. Also disclosed are pharmaceutical compns., products, and kits for the method, as well as the use of a GST-activated anticancer compd. in the manuf. of a medicament for the method. The invention further discloses a method for potentiating an anticancer therapy in a mammal, esp. a human, comprising administering a therapeutically effective amt. of a GST-activated anticancer compd. to the mammal being treated with the anticancer therapy. Further disclosed is the use of a GST-activated anticancer compd. in the manuf. of a medicament for the method. The GST-activated anticancer compd. is preferably a compd. of US Patent No. 5,556,942, and more preferably TLK286, esp. as the hydrochloride salt.

IT 50-35-1, Thalidomide 97682-44-5, Irinotecan

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)

(combination cancer therapy with GST-activated anticancer compd. and another anticancer therapy)

L132 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:737576 CAPLUS

DOCUMENT NUMBER: 139:240349

TITLE: Combination therapy including a JNK kinase inhibitor

for treating, preventing or managing proliferative disorders and cancers  
 INVENTOR(S): Stein, Bernd M.; Westwick, John K.; Ennis, Bruce W.  
 PATENT ASSIGNEE(S): Signal Pharmaceuticals, Inc., USA  
 SOURCE: PCT Int. Appl., 109 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003075917	A1	20030918	WO 2003-US6894	20030307
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004067953	A1	20040408	US 2003-384440	20030307
PRIORITY APPLN. INFO.:			US 2002-362705P	P 20020308
			US 2003-384440	A 20030307
OTHER SOURCE(S): MARPAT 139:240349				
ED Entered STN: 19 Sep 2003				
AB The invention provides methods and compns. designed for the treatment, management or prevention of cancer. The methods of the invention comprise the administration of an effective amt. of one or more inhibitors of JNK in combination with the administration of an effective amt. of one or more other agents useful for cancer therapy. The invention also provides pharmaceutical compns. comprising one or more inhibitors of JNK in combination with one or more other agents useful for cancer therapy. In particular, the invention provides methods of treatment and prevention of cancer by the administration of an effective amt. of one or more inhibitors of JNK in combination with std. and exptl. chemotherapies, hormonal therapies, bone marrow transplants, stem cell replacement therapies, biol. therapies/immunotherapies and/or radiation therapies for treatment or prevention of cancer. Also included are methods of treatment of cancer by the administration of one or more inhibitors of JNK in combination with surgery, alone or in further combination with std. and exptl. chemotherapies, hormonal therapies, bone marrow transplants, stem cell replacement therapies, biol. therapies/immunotherapies and/or radiation therapies. JNK inhibitors include e.g. indazole derivs.				
IT 50-35-1, Thalidomide 97682-44-5, Irinotecan RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (JNK kinase inhibitor in combination therapy for cancer treatment)				
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT				
L132 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN				
ACCESSION NUMBER: 2001:507528 CAPLUS				
DOCUMENT NUMBER: 135:97483				
TITLE: Composition for stabilizing and potentiating the action of anti-angiogenic substances by polyunsaturated fatty acids				
INVENTOR(S): Das, Undurti N.				

PATENT ASSIGNEE(S): EFA Sciences LLC, USA  
 SOURCE: PCT Int. Appl., 60 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001049284	A1	20010712	WO 2000-US1037	20000118
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 6380253	B1	20020430	US 2000-478291	20000105
US 2003096869	A1	20030522	US 2002-83529	20020227
US 6617354	B1	20030909	US 2002-83530	20020227

PRIORITY APPLN. INFO.: US 2000-478291 A 20000105

ED Entered STN: 13 Jul 2001

AB Disclosed is a method of stabilizing and potentiating action of mols. of known anti-angiogenic substances such as Angiostatin or Endostatin by using in coupling conjugation with cis-unsatd. fatty acids (c-UFAs) in the treatment of cell proliferative disorders uses c-UFAs chosen from linoleic acid, .gamma.-linolenic acid, dihomogamma.-linolenic acid, arachidonic acid, .alpha.-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid and cis-parinaric acid in predetd. quantities. Preferably, the c-UFAs are in the form of polyunsatd. fatty acids (PUFAs). Uncontrolled or undesirable angiogenic activity promotes cell proliferative disorders and tumor growth, which can be inhibited by the selective use of PUFAs with anti-angiogenic substances used selectively in conjunction with predetd. anti-cancer drugs. For treatment of glioma, a sodium salt of a PUFA is preferred to form an admixt. with an anti-angiogenic substance and a selected anti-cancer drug. For a non-glioma type of cell proliferation disorder, a sodium, potassium or lithium salt of a PUFA is preferred to form an admixt. with an anti-angiogenic substance. Anti-angiogenic substances envisaged in this invention include Angiostatin, Endostatin, platelet factor-4, TNP-470, thalidomide, interleukin-12 and metalloproteinase inhibitors. A preferred method of administration of the mixt. to treat a tumor is intra-arterial administration into an artery which provides the main blood supply for the tumor.

IT 50-35-1, Thalidomide

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(polyunsatd. fatty acids for **potentiating** action of anti-angiogenic substances)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L132 ANSWER 22 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004260451 EMBASE

TITLE: The role of new targeted therapies in small-cell lung cancer.

AUTHOR: Rossi A.; Maione P.; Colantuoni G.; Guerriero C.; Gridelli C.

CORPORATE SOURCE: C. Gridelli, Unita Operativa di Oncol. Medica, Azienda

SOURCE: Ospedaliera S.G. Moscati, Via Circumvallazione, 68,  
83100-Avellino, Italy. cgridelli@libero.it  
Critical Reviews in Oncology/Hematology, (2004) 51/1  
(45-53).  
Refs: 70  
ISSN: 1040-8428 CODEN: CCRHEC  
PUBLISHER IDENT.: S 1040-8428(04)00034-4  
COUNTRY: Ireland  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis  
016 Cancer  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB Lung cancer is the leading world-wide cause of cancer death. Small-cell lung cancer (SCLC) accounts for 20-25% of lung carcinomas. Chemotherapy is the cornerstone of treatment of SCLC. In limited disease, median survival is about 12-16 months with 4-5% of long-term survivors, in extensive disease median survival is 7-11 months. Improving the survival rate of patients with SCLC requires a better understanding of tumour biology and the subsequent development of novel therapeutic strategies. Several targeted agents have been introduced into clinical trials in SCLC and some phase III studies have already produced definitive results. Currently, the minority of these new agents offers a promise of improved outcomes, and negative results are more commonly reported than positive ones. To date, no targeted therapy has been approved for use in the treatment of patients with SCLC. This review will focus on the main novel biologic agents investigated in the treatment of SCLC. .COPYRG. 2004 Elsevier Ireland Ltd. All rights reserved.

L132 ANSWER 23 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2004004038 EMBASE  
TITLE: Novel chemotherapeutic agents for the treatment of glioblastoma multiforme.  
AUTHOR: Jendrossek V.; Belka C.; Bamberg M.  
CORPORATE SOURCE: V. Jendrossek, Dept. of Radiation Oncology,  
Hoppe-Seyler-Strasse 3, D-72026 Tübingen, Germany.  
verena.jendrossek@uni-tuebingen.de  
SOURCE: Expert Opinion on Investigational Drugs, (2003) 12/12  
(1899-1924).  
Refs: 248  
ISSN: 1354-3784 CODEN: EOIDER  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 008 Neurology and Neurosurgery  
016 Cancer  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB During the last few decades, the discovery of novel targets for therapeutic intervention led to the development of chemotherapeutic agents that specifically interfere with altered cellular functions of tumour cells. Genetic alterations in glioblastoma affect cell proliferation and cell cycle control, as well as invasive and metastatic growth. Therefore, innovative therapeutic strategies have been based on drugs targeting cellular proliferation, invasion, angiogenesis, metastasis and differentiation of tumour cells. Furthermore, disruption of cell-death

pathways also contributes to the pathogenesis of glioblastoma and may result in resistance to chemotherapy and radiation. Therefore, additional treatment strategies that target intracellular survival and/or apoptotic pathways are under current laboratory investigation. The progress in the understanding of glioblastoma tumour biology and the refined diagnosis of individual patients together with the exploration of targeted drugs may allow a risk-adapted, individualised therapeutic strategy and will hopefully improve prognosis of glioblastoma patients in the future.

L132 ANSWER 24 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2003189602 EMBASE  
TITLE: Cancer Drug Development: New Directions and Challenges -  
SMi Conference: 10-11 March 2003, London, UK.  
AUTHOR: Erlich R.  
CORPORATE SOURCE: R. Erlich, Thomson Current Drugs, Middlesex House, 34-42  
Cleveland Street, London W1T 4LB, United Kingdom.  
rebecca.erlich@current-drugs.com  
SOURCE: IDrugs, (1 Apr 2003) 6/4 (331-333).  
ISSN: 1369-7056 CODEN: IDRUFN  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 016 Cancer  
037 Drug Literature Index  
030 Pharmacology  
029 Clinical Biochemistry  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Over the last five years, the explosion in knowledge at the molecular level in areas such as signal transduction and the cell cycle has revealed a plethora of molecular targets potentially involved in the pathogenesis of cancer. Cancer drug development is now reflecting the emerging molecular archaeology of the disease and lessons are already being learned from targeted therapies, such as gefitinib (Iressa; AstraZeneca plc), that have not achieved the expected benefits when used in combination with conventional chemotherapy in late-stage clinical trials. The disappointment with Iressa, a therapy that inhibits EGFR, has highlighted the need to rethink clinical trial designs and target populations that will benefit from such treatments. Clinical success with Celgene Corp's thalidomide (Thalomid) has demonstrated that lack of response in animals cannot reliably be extrapolated to predict the efficacy of a drug in patients. However, in the current arena of cancer therapy, it is highly unusual for a drug to reach the market where clinical responses have not been observed in phase I trials, even though this endpoint is not strictly a defining characteristic of the classic phase I trial. To achieve the full benefit from clinical trials with targeted therapies, it will be necessary to demonstrate the activity of the drug through the definition of biomarkers that are present in blood or urine and are therefore easily accessible for assay. A theme echoed throughout the 2 days of the meeting was the necessity to validate biomarkers at the preclinical stage, followed by the need to develop assays that work in the patient. Karol Sikora (AstraZeneca plc, UK), who chaired day one of the meeting proceedings, pointed out that new style phase I trials must find the dose of a drug that inhibits its target, and that the development of the technology to do so will require closer collaborations between academia, biotechnology and 'big pharma'.

L132 ANSWER 25 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2004016813 EMBASE  
TITLE: The Combination of Antiangiogenic and Cytotoxic Agents in



the Treatment of Prostate Cancer.  
AUTHOR: Retter A.S.; Figg W.D.; Dahut W.L.  
CORPORATE SOURCE: Dr. W.L. Dahut, Med. Oncology Clinical Research Unit,  
Center for Cancer Research, National Cancer Institute, 10  
Center Dr, Bethesda, MD 20892, United States.  
dahutw@mail.nih.gov  
SOURCE: Clinical Prostate Cancer, (2003) 2/3 (153-159).  
Refs: 59  
ISSN: 1540-0352 CODEN: CPCLC4  
COUNTRY: United States  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 016 Cancer  
028 Urology and Nephrology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB Metastatic prostate cancer is one of the leading causes of cancer death in men. Although initially responsive to hormone therapy, it eventually progresses in almost all patients. For this reason, there has been a search for novel agents to use in the fight against androgen-independent prostate cancer. Antiangiogenesis is a relatively new antitumor strategy that has been employed in the treatments of many malignancies. As prostate cancer is likely dependent on angiogenesis for its growth and progression, it would logically serve as a good target for this modality. Initially met with great enthusiasm, antiangiogenic drugs have seen only limited success when used as single agents. This has been attributed to many possible etiologies including lack of cytotoxicity and use in situations of large tumor burden. In order to overcome these problems, many investigators are combining antiangiogenic agents with more traditional cytotoxic chemotherapy regimens in hope of augmenting the effects of either drug alone. This article will review the background of angiogenesis inhibition and the use of such combinations in metastatic prostate cancer.

L132 ANSWER 26 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2002231291 EMBASE  
TITLE: Pharmacological strategies to increase the antitumor activity of methylating agents.  
AUTHOR: Tentori L.; Graziani G.  
CORPORATE SOURCE: G. Graziani, Department of Neuroscience, University of Rome Tor Vergata, Via Montpellier 1, 00133 Rome, Italy.  
graziani@uniroma2.it  
SOURCE: Current Medicinal Chemistry, (2002) 9/13 (1285-1301).  
Refs: 160  
ISSN: 0929-8673 CODEN: CMCHE7  
COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 016 Cancer  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
052 Toxicology  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB Among methylating agents of clinical interest, temozolomide is a novel antitumor compound that has raised particular interest due to its acceptable safety profile and activity against tumors poorly responsive to conventional chemotherapy, such as malignant glioma and metastatic melanoma. Moreover, the drug has recently shown promising antitumor activity in a patient affected by primary brain lymphoma and is currently under phase II clinical trials for leptomeningeal metastases from leukemia

and lymphoma or for brain metastases from lung and breast cancers. The antitumor activity of TMZ, that generates different types of methyl adducts (70% N7-methylguanine, 10% N3-methyladenine and 9% O(6)-methylguanine), has been mainly attributed to the formation of O(6)-methylguanine adducts. Indeed, tumor cell susceptibility to TMZ is strongly affected by the functional status of DNA repair systems, involved either in the removal of methyl adducts from O(6)G or in the apoptotic signaling triggered by O(6)-methylG:T mispairs. This review will focus on the different pharmacological strategies aimed at overcoming tumor resistance to TMZ such as new formulations of the drug or dosing schedules, and combined treatments with other chemotherapeutic agents, modulators of DNA repair systems, or gene therapy. The potential use of N3-methyladenine selective agents in the case of tumors tolerant to O(6)-methylguanine will be also discussed.

L132 ANSWER 27 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2002169645 EMBASE  
TITLE: Thalidomide in cancer treatment: A potential role in the elderly?.  
AUTHOR: Zhou S.; Kestell P.; Tingle M.D.; Paxton J.W.  
CORPORATE SOURCE: S. Zhou, Division of Pharmacology, Faculty of Medical Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand. shufeng.zhou@auckland.ac.nz  
SOURCE: Drugs and Aging, (2002) 19/2 (85-100).  
Refs: 164  
ISSN: 1170-229X CODEN: DRAGE6  
COUNTRY: New Zealand  
DOCUMENT TYPE: Journal; **General Review**  
FILE SEGMENT: 016 Cancer  
020 Gerontology and Geriatrics  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB There is increased interest in the treatment of cancer with thalidomide because of its antiangiogenic, immunomodulating and sedative effects. In animal models, the antitumour activity of thalidomide is dependent on the species, route of administration and coadministration of other drugs. For example, thalidomide has shown antitumour effects as a single agent in rabbits, but not in mice. In addition, the antitumour effects of the conventional cytotoxic drug cyclophosphamide and the tumour necrosis factor inducer 5,6-dimethylxanthene-4-acetic acid (DMXAA) were found to be potentiated by thalidomide in mice bearing colon 38 adenocarcinoma tumours. Further studies have revealed that thalidomide up-regulates intratumoral production of tumour necrosis factor- $\alpha$ . 10-fold over that induced by DMXAA alone. Coadministration of thalidomide also significantly reduced the plasma clearance of DMXAA and cyclophosphamide. All these effects of thalidomide may contribute to the enhanced antitumour activity. Recent clinical trials of thalidomide have indicated that it has minimal anticancer activity for most patients with solid tumours when used as a single agent, although it was well tolerated. However, improved responses have been reported in patients with multiple myeloma. Palliative effects of thalidomide on cancer-related symptoms have also been observed, especially for geriatric patients with prostate cancer. Thalidomide also eliminates the dose-limiting gastrointestinal toxic effects of irinotecan. There is preliminary evidence indicating that the clearance of thalidomide may be reduced in the elderly. The exact role of thalidomide in the treatment of cancer and cancer cachexia in the elderly remains to be elucidated. However, it may have some value as part of a multimodality anticancer therapy, rather than as a single agent.

L132 ANSWER 28 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2002068674 EMBASE  
TITLE: Thalidomide in cancer.  
AUTHOR: Singhal S.; Mehta J.  
CORPORATE SOURCE: S. Singhal, Division of Hematology, Northwestern Univ.  
Medical School, Robert H. Lurie Can. Ctr. NW Univ., 676 N  
St. Clair Street, Chicago, IL 60611, United States.  
s-singhal@northwestern.edu  
SOURCE: Biomedicine and Pharmacotherapy, (2002) 56/1 (4-12).  
Refs: 61  
ISSN: 0753-3322 CODEN: BIPHEX  
PUBLISHER IDENT.: S 0753-3322(01)00146-9  
COUNTRY: France  
DOCUMENT TYPE: Journal; **General Review**  
FILE SEGMENT: 016 Cancer  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Thalidomide has immunomodulatory and anti-angiogenic properties which may underlie its activity in cancer. After its success in myeloma, it has been investigated in other plasma cell dyscrasias, myelodysplastic syndromes, gliomas, Kaposi's sarcoma, renal cell carcinoma, advanced breast cancer, and colon cancer. Thalidomide causes responses in 30-50% of myeloma patients as a single agent, and acts synergistically with corticosteroids and chemotherapy. Thalidomide results in the reduction or elimination of transfusion-dependence in some patients with myelodysplastic syndrome. Responses have also been seen in one-third of patients with Kaposi's sarcoma, in a small proportion of patients with renal cell carcinoma and high-grade glioma, and in some patients with colon cancer in combination with irinotecan. The drug is being investigated currently in a number of clinical trials for cancer. Drowsiness, constipation, and fatigue are common side effects, whereas peripheral neuropathy and skin rash are seen in one-third. A minority of patients experience bradycardia. Thrombotic phenomena are especially common when thalidomide is combined with chemotherapy. Adverse effects severe enough to necessitate cessation of therapy are seen in around 20% of patients. A therapeutic trial of thalidomide is essential in all patients with relapsed or refractory myeloma. In other cancers, the best way to use the drug is in the setting of clinical trials. In the absence of access to studies or alternative therapeutic options, thalidomide could be considered singly or in combination with standard therapy. .COPYRGHT. 2002 Editions scientifiques et medicales Elsevier SAS.

L132 ANSWER 29 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2001329787 EMBASE  
TITLE: Thalidomide: An old sedative-hypnotic with anticancer activity?.  
AUTHOR: Gasparini G.; Morabito A.; Magnani E.; Gattuso D.;  
Capaccetti B.; Alberti A.M.  
CORPORATE SOURCE: G. Gasparini, Division of Medical Oncology, Azienda  
Complesso Ospedaliero, Via Martinotti 20, 00135 Rome,  
Italy. gasparini.oncology@tiscalinet.it  
SOURCE: Current Opinion in Investigational Drugs, (2001) 2/9  
(1302-1308).  
Refs: 63  
ISSN: 0967-8298 CODEN: CIDREE  
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 037 Drug Literature Index  
030 Pharmacology  
038 Adverse Reactions Titles  
016 Cancer  
008 Neurology and Neurosurgery  
028 Urology and Nephrology  
048 Gastroenterology  
011 Otorhinolaryngology  
029 Clinical Biochemistry  
014 Radiology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Thalidomide is a synthetic derivative of glutamic acid with sedative-hypnotic activity, which caused devastating teratogenic effects in the 1960s. This paper reviews the possible mechanisms of its teratogenic effect, its new therapeutic indications, the proposed mechanisms for its antitumor activity and, finally, reviews published studies of its application in oncology. Current data demonstrates that thalidomide is clinically promising in multiple myeloma, glioblastoma multiforme and renal cell cancer. Furthermore, a beneficial effect of the drug has been proposed in cancer-related cachexia, which merits further investigation. Well-designed, randomized studies are warranted to establish the possible indications of thalidomide as an antitumor compound.

L132 ANSWER 30 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2001277717 EMBASE  
TITLE: The revitalization of thalidomide.  
AUTHOR: Thomas D.A.; Kantarjian H.M.  
CORPORATE SOURCE: D.A. Thomas, Department of Leukemia, M.D. Anderson Cancer Center, Houston, TX, United States  
SOURCE: Annals of Oncology, (2001) 12/7 (885-886).  
Refs: 30  
ISSN: 0923-7534 CODEN: ANONE2  
COUNTRY: Netherlands  
DOCUMENT TYPE: Journal; Editorial  
FILE SEGMENT: 005 General Pathology and Pathological Anatomy  
016 Cancer  
025 Hematology  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English

L132 ANSWER 31 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2002227234 EMBASE  
TITLE: New agents for the treatment of renal cell carcinoma.  
AUTHOR: Tian G.G.; Dawson N.A.  
CORPORATE SOURCE: N.A. Dawson, Division of Hematology and Oncology, Greenebaum Cancer Center, University of Maryland, 22 South Greene Street, Baltimore, MD 21201, United States.  
ndawson@umm.edu  
SOURCE: Expert Review of Anticancer Therapy, (2001) 1/4 (546-554).  
Refs: 97  
ISSN: 1473-7140 CODEN: ERATBJ  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 016 Cancer  
028 Urology and Nephrology

030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB One-third of patients with renal cell carcinoma present with unresectable or metastatic disease. Immunotherapy, the current standard treatment, induces response in only 10-20% of patients. Chemotherapy with current agents is minimally effective. Other approaches including allogeneic stem cell transplant, vaccine and gene therapy and signal transduction inhibitors, offer promise in early Phase studies. This paper reviews the current treatment options and promising new agents in development.

L132 ANSWER 32 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2002227178 EMBASE

TITLE: Temozolomide: A novel oral alkylating agent.

AUTHOR: Danson S.J.; Middleton M.R.

CORPORATE SOURCE: M.R. Middleton, Department of Medical Oncology, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 9BX, United Kingdom. mmiddleton@picr.man.ac.uk

SOURCE: Expert Review of Anticancer Therapy, (2001) 1/1 (13-19).  
 Refs: 50

ISSN: 1473-7140 CODEN: ERATBJ

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 008 Neurology and Neurosurgery  
 013 Dermatology and Venereology  
 016 Cancer  
 037 Drug Literature Index  
 038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Temozolomide is an imidazotetrazine with a mechanism of action and efficacy similar to dacarbazine (DTIC). However, it differs from DTIC in that it can be taken orally, degrades spontaneously to an active metabolite and penetrates the blood-brain barrier. It is well tolerated, making it a suitable candidate for combination chemotherapy. Trials to date have focussed on its activity in advanced metastatic melanoma and high-grade malignant glioma. Investigations into other indications, in particular solid tumors with central nervous system metastases, are ongoing. Studies of new drug schedules and of drugs to ameliorate temozolomide resistance offer the prospect of increased efficacy.

L132 ANSWER 33 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.  
 on STN

ACCESSION NUMBER: 2000374422 EMBASE

TITLE: A review of angiogenesis and antiangiogenic therapy with thalidomide in multiple myeloma.

AUTHOR: Rajkumar S.V.; Witzig T.E.

CORPORATE SOURCE: Dr. S.V. Rajkumar, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States.  
 rajks@mayo.edu

SOURCE: Cancer Treatment Reviews, (2000) 26/5 (351-362).  
 Refs: 99

ISSN: 0305-7372 CODEN: CTREDJ

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; **General Review**

FILE SEGMENT: 016 Cancer  
 025 Hematology  
 030 Pharmacology  
 037 Drug Literature Index

038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Angiogenesis is the formation of new blood vessels and occurs physiologically during embryonal growth, wound healing and during the menstrual cycle. It is essential for the proliferation and metastases of most malignant neoplasms. Recent evidence suggests that angiogenesis is increased in multiple myeloma and has prognostic value in the disease. Angiogenic cytokines such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor are expressed by myeloma cells and appear to play a role in the increased angiogenesis seen in myeloma. In addition, VEGF may serve as a paracrine growth factor for myeloma cells. Based on the increased angiogenesis observed in myeloma, thalidomide has been studied as antiangiogenic therapy. Although its mechanism of action in myeloma is still unclear thalidomide appears to be active in 25-30% of patients with refractory myeloma. Major toxicities include constipation, sedation, skin rash, fatigue, and peripheral neuropathy. Studies are ongoing to determine its role as initial treatment for myeloma. This paper reviews the available data on angiogenesis in myeloma, and summarizes the role of thalidomide therapy in this disease. The pharmacology and toxicity of thalidomide are also discussed. (C) 2000 Harcourt Publishers Ltd.

FILE 'HOME' ENTERED AT 13:17:50 ON 20 JUL 2004